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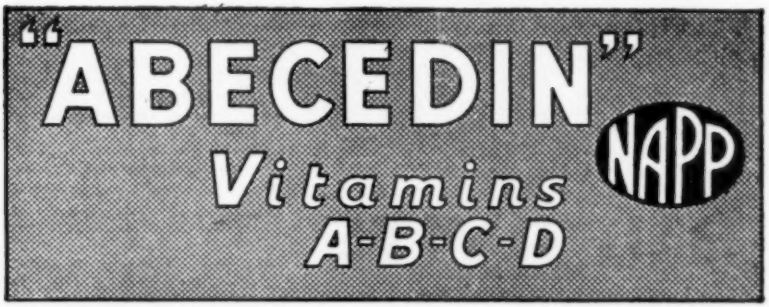

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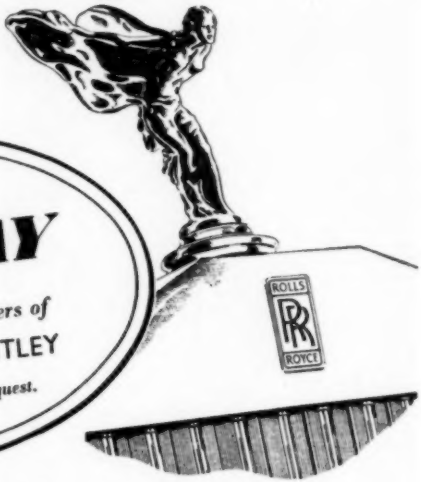

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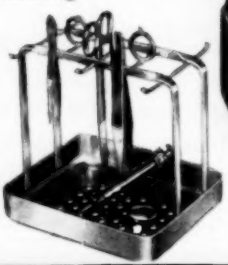

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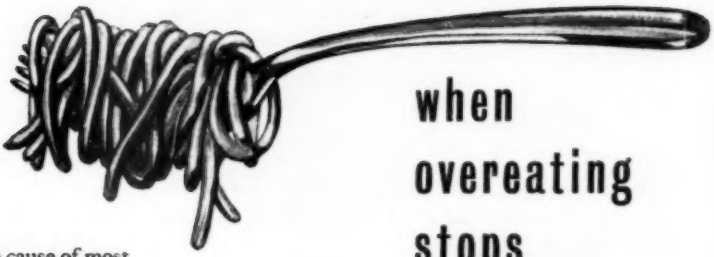

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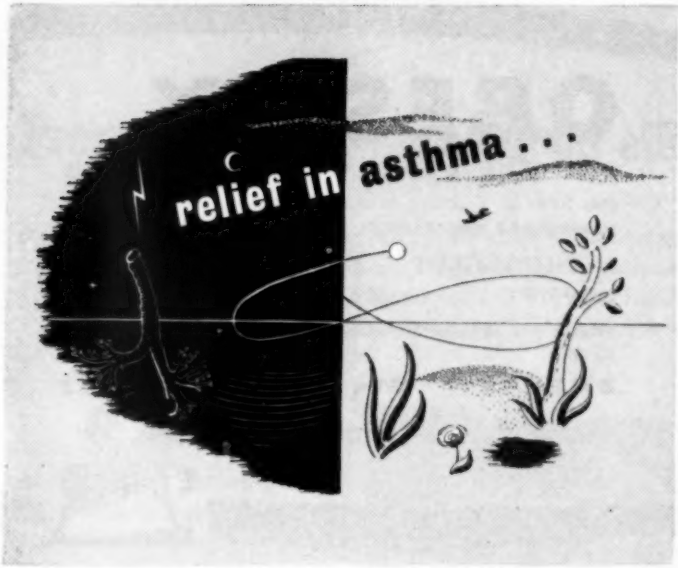

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TRADE MARK — Trichloroethylene

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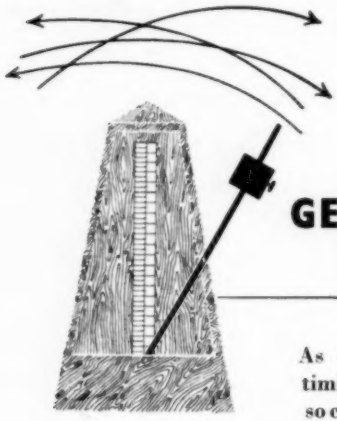

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Experience has shown that Liquid Derbac is *100% efficient* in the treatment of pediculosis capitis. One application is fully effective and eradication is complete *within the hour*. Treatment is simple and clean. Liquid Derbac, a D.D.T. emulsion, which is non-toxic and non-irritant, is used by clinics all over the British Isles. 40 oz. bottle 10/8d 2 oz. bottle 1/10d. Literature sent on request.

* See The British Medical Journal, 24th August, 1946.

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now contains the more stable crystalline potassium penicillin G

In established nasal infections

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penicillin-vasoconstrictor combination for intranasal use

'Pendex' presents, in a stable aqueous solution, the potent antibacterial action of penicillin combined with the rapid and prolonged vasoconstriction of 'Paredrinex'. The superior penetrative action of penicillin, aided by a vasoconstrictor, makes 'Pendex' a valuable local treatment in established nasal infections where the organisms are often too deeply embedded to be exposed to the killing effects of surface acting drugs.

When prepared as directed 'Pendex' will contain, for one week at room temperature, not less than: Crystalline potassium penicillin G, 1,500 International Units per ml.; 'Paredrinex', 1 per cent.; in a specially buffered aqueous solution.

The 'Pendex' package consists of penicillin in dry state and a buffered aqueous solution of 'Paredrinex'—each in a separate container. The pharmacist has only to mix the two, and 'Pendex' is dispensed freshly prepared and with the penicillin at full therapeutic potency.

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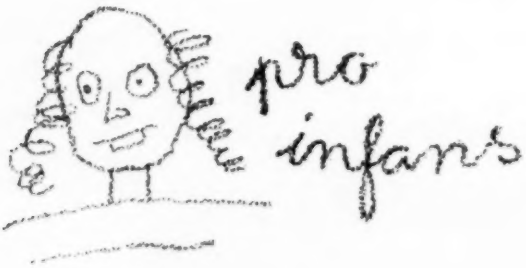

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FREE PROFESSIONAL SAMPLES, sufficient for a good trial with your difficult babies are available to Members of the Medical Profession. Write to Sister Lauras Food Co., Ltd. (Dept. PRA/33), Springfield Works, Bishopbriggs, Near Glasgow.

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Relief from hæmorrhoids with non-anæsthetic drugs

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NOT A PENNY LOST IN 100 YEARS!

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He knows what's good for him when he's feeling exhausted after a tiring day: for inducing complete relaxation and sound, health-giving sleep, it's

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the original British procaine penicillin G
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procaine penicillin G **plus** crystalline penicillin G
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good feeding for better health

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MARMITE

yeast extract

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RIBOFLAVIN (*vitamin* B_2) 1.5 mg. per oz. NIACIN (*nicotinic acid*) 16.5 mg. per oz.

Jars: 1-oz. 8d., 2-oz. 1/1, 4-oz. 2/-, 8-oz. 3/3, 16-oz. 5/9. Obtainable from Chemists and Grocers

Special terms for packs for hospitals, welfare centres and schools

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509 *Literature on application*

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a stable solution of **Iodide of Caffeine** *in a special medium*

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Condition of prolapsed organs supported with front-laced corset.

An example of how successfully Spirella cares for figure defects and abnormal physical conditions.

The Spirella way to health is the beautifying and comfortable way—by natural support, correctly applied to the individual figure.

There are Spirella Corsetieres everywhere, nearly 5,000 of them. Names and addresses can be ascertained from

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In Hysteria and Psychasthenia it relieves nervous excitement and produces a calm state of mind that is conducive to rapid recovery. It is also of value in states of temporary emotional excitement, in Hypochondriasis and Melancholia.

DOSAGE: One tablespoonful in water twice or thrice daily.
As a hypnotic: Two tablespoonfuls at bedtime.

Supplied in bottles of 187 c.c., and 16 oz., also in Dispensing Packs of 40 oz. and 80 oz.

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Tuberculosis

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is usually accompanied by excessive night sweating, palpitations, nervous diarrhœa, anorexia and psychic depression which may be regarded as signs of autonomic nervous hyperexcitation. These symptoms may retard recovery or even aggravate the condition.

BELLERGAL

has proved effective in controlling these disturbances and in restoring the autonomic nervous equilibrium. Each tablet contains 0.1 mg. Bellafoline, a vagolytic, 0.3 mg. Femergin, a sympathicolytic and 20 mg. phenobarbitone, a sedative of the autonomic nervous centres in the brain stem.

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Large Annular Ulcer

Healed after 24 years' duration

CASE HISTORY: C.W.—Night Watchman aged 61 years.

Large annular ulcer of 24 years' duration on lower third of R. leg. Œdematous edges and unhealthy base—much surrounding eczema.

4th May. No varicose veins visible or palpable. Ulcer insufflated with Penicillin and Sulphathiazole powder. An Elastoplast Bandage was applied with considerable compression over a stirrup of the same material applied to the internal and external aspects of the leg.

At first the bandage was changed at weekly intervals because the ulcer discharged freely and the œdema was considerable.

From June onwards the bandage was changed fortnightly and at each change the ulcer had an improved appearance and decreased area.

14th Dec. Ulcer healed completely, with skin and leg now of normal appearance.

COMMENT: The patient was never laid up and continued his work during the whole period of treatment.

These details and illustrations are of an actual case. T. J. Smith and Nephew Ltd., of Hull, publish this instance—typical of many in which their products have been used with success.

Elastoplast Elastic Adhesive Bandages are available in widths of 2", 2½", 3" and 4" x 5/6 yds. long when stretched.

ELASTOPLAST BANDAGES *are manufactured by* **T. J. SMITH & NEPHEW, LTD., HULL**

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New Type of Skin Balm

"A superior preparation"

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"Valderma Antiseptic Balm exerted the most consistent bacteriostatic effect of all the preparations tested.

"From the 'in vitro' experiments it was clearly evident that owing to the effectiveness of the two bacteriostatic agents, and the ideal nature of the oil-in-water base employed in Valderma Antiseptic Balm, optimum conditions had been created which made this preparation superior to any other examined."

The organisms used for these tests were Staph. aureus, Staph. albus, Strep. viridans, B. coli, and B. megatherium. Doctors who are interested can obtain complete data from Valderma Laboratories, Research Division P2, 17, Berners Street, London, W.1.

Valderma *oil-in-water emulsion base*

Here's metal more attractive

HAMLET, ACT III, SCENE II

IRON in readily assimilable form is the metal so vital for the successful treatment of hypochromic anæmias.

Of the iron compounds usually given by mouth, ferrous sulphate is generally recognised as the most effective.

In 'PLASTULES,' ferrous sulphate is presented in its most attractive form—as a semi-fluid in a capsule which rapidly dissolves in the stomach, thus ensuring maximum absorption. 'PLASTULES' induce a rapid response without gastric upset.

'PLASTULES' are available in four varieties: Plain; with Liver Extract; with Folic Acid; and with Hog's Stomach.

'Plastules'
Trade Mark
Hæmatinic Compound

JOHN WYETH & BROTHER, LIMITED
CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1

Wyeth

P. A. S. (PARA-AMINOSALICYLIC ACID)

for Ambulatory Treatment of Pulmonary Tuberculosis

The sodium salt of P.A.S. (Sodium P.A.S.) is being increasingly used both alone and in conjunction with Streptomycin for tuberculosis in ambulant patients awaiting admission to Sanatoria. Since solutions of sodium P.A.S. should be freshly prepared, this necessitates frequent visits by the Patients to the Pharmacist.

To avoid this inconvenience and also to ensure that the Patients take solutions of sodium P.A.S. before discolouration and decomposition, which increases intolerance, we supply cartons of 48 packets, each containing an individual dose of sodium P.A.S. The contents of each packet are dissolved in water by the Patients themselves and the freshly-prepared solution is taken at prescribed intervals.

Sodium P.A.S. is available in the following forms :—

Powder	Ampoules 20% solution	Tablets		Packets
		0.41 gm. ≡ 0.3 gm. P.A.S.	0.69 gm. ≡ 0.5 gm. P.A.S.	4.1 gm. 5 gm.
100, 250, 500, 1,000 gm.	Boxes of 5 x 5 c.c. ,, ,, 5 x 10 c.c.	100 500 1,000	100 500 1,000	Cartons of 48

Detailed literature is available on request

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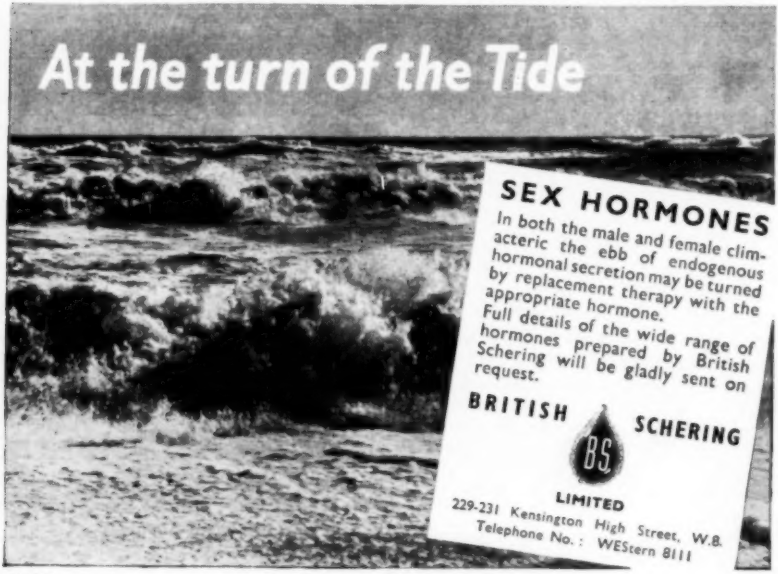
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SUMMER DIARRHŒA!

'Cremosuxidine' contains:—

Sulfasuxidine	10%
Pectin	1%
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'Cremosuxidine' is an extremely palatable chocolate-mint flavoured suspension designed particularly for the control of diarrhœa.

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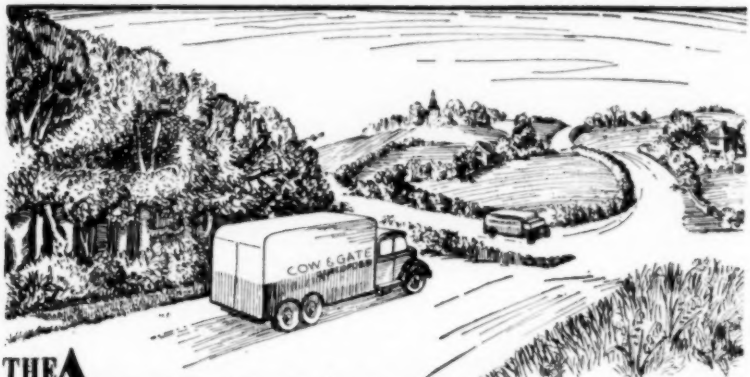
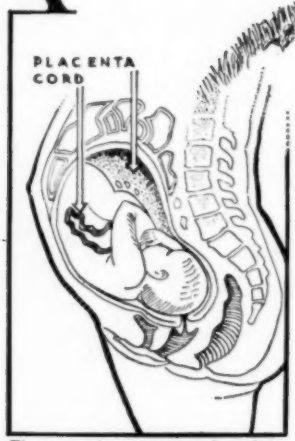


THE ARTERIALS of LIFE



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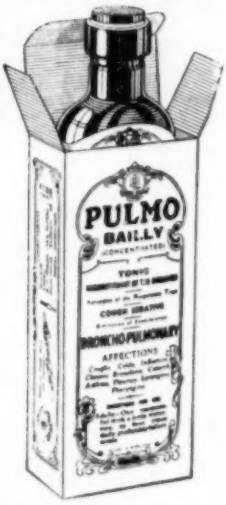

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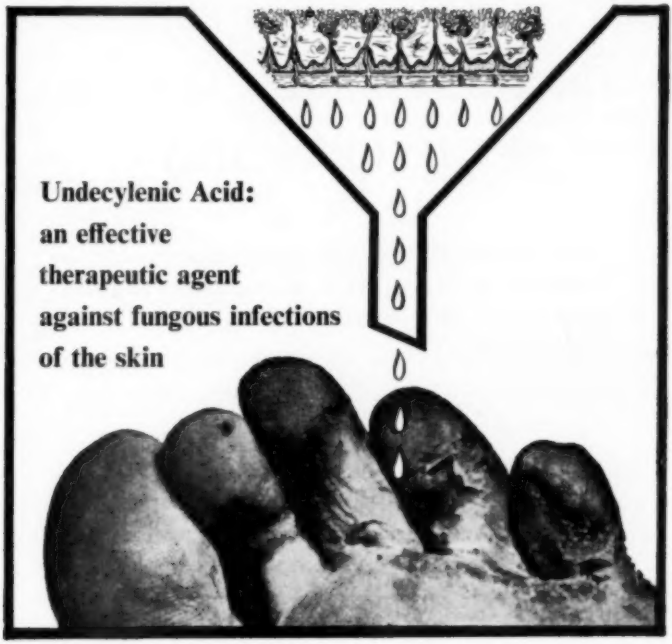

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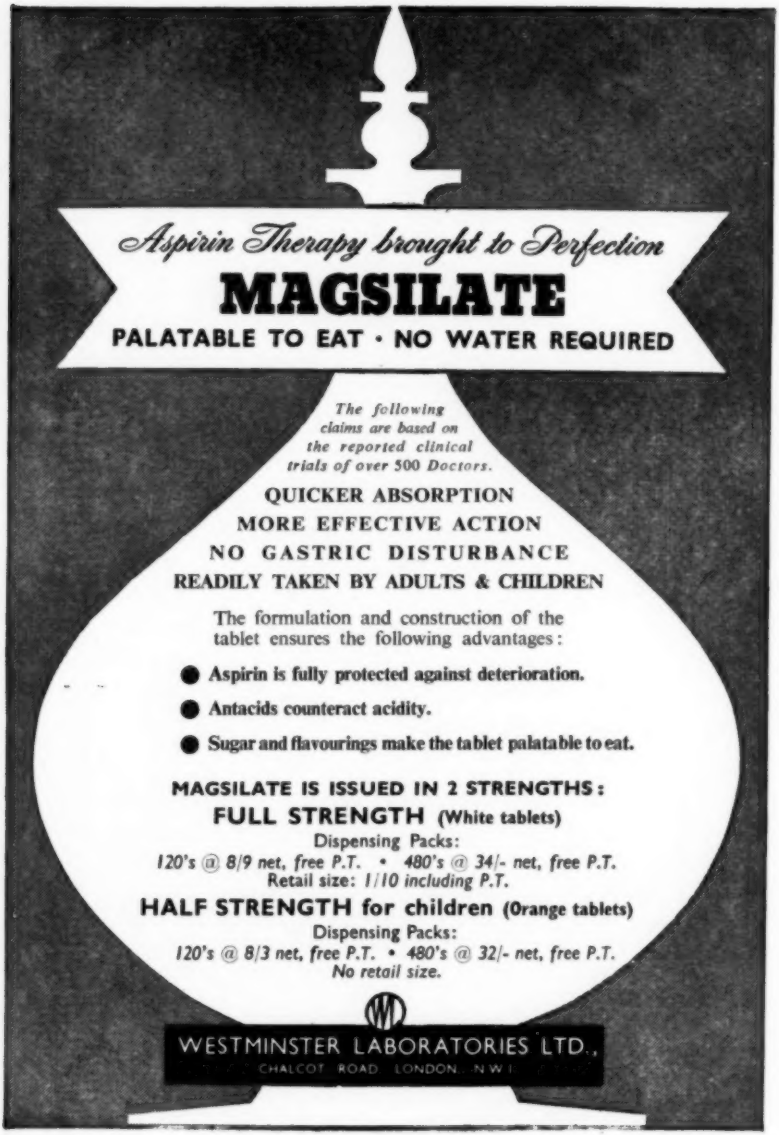
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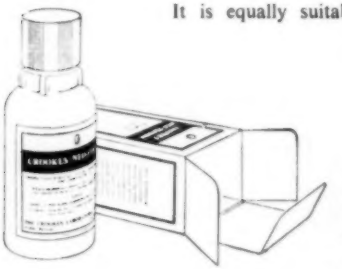

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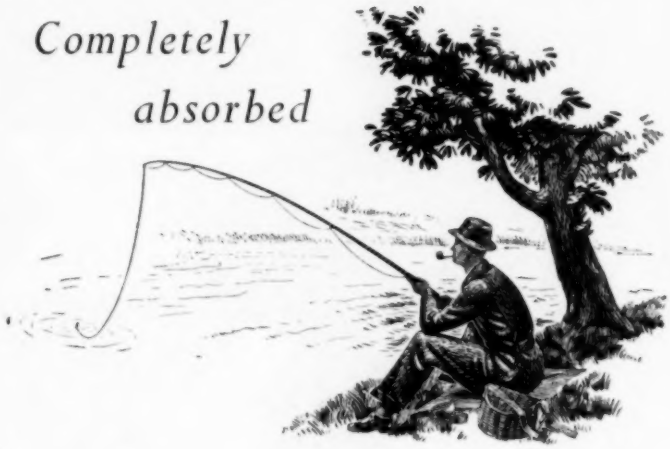

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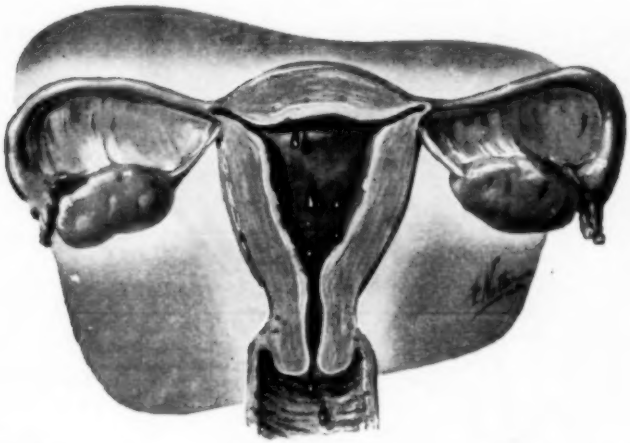

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THE PRACTITIONER

No. 987 SEPTEMBER 1950 Volume 165

THE MONTH

The Symposium

In no disease are preventive and curative medicine more closely interlinked than in the case of tuberculosis. Unless the incidence of the disease is known, prophylactic and curative measures will not be integrated to the fullest advantage. In all three aspects—detection, prevention, and treatment—rapid advances have been achieved during the last decade. Only for some of these has it been possible to find space in the symposium this month. The trends of both morbidity and mortality are authoritatively outlined by Dr. Percy Stocks. Mass miniature radiography, now a firmly established means of detection, is reviewed by Dr. S. H. Graham of Cardiff. Tuberculin as a diagnostic agent has had a long, and at times chequered, career, and this is critically reviewed by Liverpool workers. Whilst chemotherapy is the most dramatic advance in the field of treatment, its development has been accompanied by an increasing scope for surgery, and both these aspects of therapy are reviewed by experts in their respective fields. Almost as dramatic as the introduction of streptomycin is that of calciferol for the treatment of lupus vulgaris, and it is therefore only reasonable that the whole subject of tuberculosis of the skin should be reviewed in this number. Genito-urinary tuberculosis is an outstanding example of tuberculous infection in which the introduction of chemotherapy has rendered cooperation between physician and surgeon of increasing importance—a point well brought out in the article by Mr. David Band.

The Antibiotic Trail

The latest addition to the list of active antibiotics is 'terramycin', which is obtained from an actinomycete, *Streptomyces rimosus*. Preliminary reports indicate that it is well tolerated and free from serious toxic properties. It has the further advantage of being active when taken by mouth. The usual dosage is 2 to 3 grammes daily, in divided doses every six hours. It diffuses rapidly through the placenta and into the pleural cavity, but apparently not into the cerebrospinal fluid. Its bacterial spectrum is extensive, including most bacillary infections, many coccal infections, and rickettsial infections. The possibility of its being active in amœbiasis is suggested by some preliminary reports, but these will require careful confirmation. Two organisms against which it appears to have little effect are *B. typhosus* and *Ps. pyocyaneus*. It would certainly appear as if terramycin were a useful adjunct to the available

antibiotics. Its relative value, *vis-a-vis* aureomycin, can only be established by prolonged clinical use, but its stability may prove to be one of its major practical advantages. We believe that the makers have already placed an elixir of terramycin on the market.

Sugar and Caries

Of all the many theories advanced to explain the causation of dental caries, the most persistent is undoubtedly that which associates it with an excessive intake of sugar. With increasing knowledge of the condition the experts are becoming more guarded in their views on the subject, and it is becoming more and more evident that, in the present state of our knowledge, no one factor can be held responsible. This was well brought out at a discussion on 'sugar and dental caries' recently held by the California State Dental Association, the proceedings of which have been published as a special issue of the *Journal of the California State Dental Association* (May-June 1950). One of the most interesting contributions to this symposium was a report indicating that in rats, hamsters and monkeys a high-sugar diet is not accompanied by the development of caries unless the diet is fed to the animals during the time that their teeth are developing. This observation is correlated with the reports from Europe that there was a decrease in the incidence of dental caries during the 1939-45 war, as it is suggested that this decrease only occurred in younger children whose teeth were developing during the period of low sugar intake. The one definite conclusion that can be drawn from this symposium is that much further work requires to be done before a definite opinion can be given on this vexed subject. It is certainly not a simple question of reducing sugar intake, or of giving fluorides, or of using ammoniated dentifrices. One or more of these may be of value, but the structure of the teeth must be given prior consideration, and clearly much needs to be done on this problem alone. The ordinary clinician is increasingly impressed by the evidence that antenatal and infant dietetic influences may be of paramount importance.

Hansard and Terminology

To impugn the accuracy of 'Hansard' may be verging on *lèse-majesté*, but its use of 'tubercular' for 'tuberculous' cannot be allowed to pass unnoticed. In extenuation of this regrettable error it must be confessed that the medical profession is not above criticism, and even *The Times* has been known to fall from grace. 'Tubercular', of course, is the adjective to describe that pertaining to a small rounded projection or nodule, whilst 'tuberculous' means pertaining to tuberculosis. This distinction is recognized by the 'Shorter Oxford English Dictionary', and is observed by all the standard medical textbooks in the English language. Indeed, the latest edition of the 'New Gould Medical Dictionary' goes so far as to state that 'tubercular' is often used erroneously for 'tuberculous'. With long usage and the backing of the 'O.E.D.' to support the distinction, it is to be hoped that the editors of

'Hansard' will see their way to come into line and in future will use 'tuberculous' when they are referring to anything associated with tuberculosis. As Dr. J. M. Hamill pointed out some years ago, 'the distinction may appear to be meticulous, but precision in language makes for clarity of thought and exposition, and the reader of an article is entitled to expect this from the writer'.

A Rheumatic 'Remedy'

IT is clear that any remedy that offers fresh hope to the patient with chronic rheumatism who 'had suffered many things of many physicians, and had spent all that she had, and was nothing bettered, but rather grew worse', is going to pay rich dividends. It is only fair to such a patient to point out that rubbing in tooth pastes, strawberry jam or axle grease will do her rheumatics just as much good as applying adrenaline cream, at far less cost, if she applies it with equal faith. Behind the claims for this latest 'cure' lies one of the oldest therapeutic fallacies in the world: that when some new and effective remedy appears on the medical horizon, any other substance resembling it in name or in source must be equally marvellous. Compound E, a substance derived in minute quantities from the adrenal cortex, has been shown to ameliorate rheumatoid arthritis, temporarily at any rate; therefore 'adrenaline cream' appears as a 'cure' for rheumatism. Research work on the rheumatic diseases is proceeding in every civilized country. The cure will come one day, but when it comes it will be the result of close cooperation between experienced clinicians and laboratory workers; it will be backed by reasoned evidence and supported by scientific experiment.

Statistics Simplified

ALTHOUGH we are not informed whether Julius Cæsar had a consultant statistician, he certainly had the statistician's outlook on life when he remarked that '*fere libenter homines id quod volunt credunt*' (men willingly believe what they wish). Not altogether without reason, the medical profession has been slow to accept the statistician as a colleague, particularly in clinical trials of new therapeutic substances. Today, however, it is generally agreed that, used accurately and with common sense, statistics are a valuable ally to medicine. For the practitioner who wishes to understand the subject but who is terrified at the mere mention of mathematics, Professor Bradford Hill has supplied an introduction to the subject which is ideal ('Principles of Medical Statistics', by A. Bradford Hill, D.Sc., Ph.D., fifth edition. London: *The Lancet* Ltd., 1950. Price 10*s*. 6*d*.). With a minimum of technical terms and an outstanding gift for lucid exposition, the author presents an outline of medical statistics which no one with a modicum of mathematical knowledge can fail to understand. The mere fact that his book has reached a fifth edition within thirteen years is a striking tribute to its value. To those who have read the book there is no need to commend it; to all others it can be highly recommended as the best introduction to the subject which exists at the moment in the English language.

VITAL STATISTICS OF TUBERCULOSIS IN ENGLAND AND WALES

By PERCY STOCKS, C.M.G., M.D., F.R.C.P.
Chief Medical Statistician, General Register Office.

MORTALITY statistics of tuberculosis in Great Britain have received a good deal of attention since the last symposium on the subject in *The Practitioner*, which included an article on mortality and morbidity (Stocks, 1944). Not much information of a statistical kind has been published concerning morbidity beyond the annual totals of notifications by sex and age for respiratory tuberculosis, and of the findings in mass radiography surveys, in England and Wales as a whole, appearing in the Annual Reports of the Ministry of Health. A comparison was made, however, between rates in the adult population derived from priority allowances of milk based on medical certification and from the Survey of Sickness (Stocks, 1949a). The comparison showed that at the end of 1947, apart from patients in hospitals and sanatoria, 278 people of all ages per 100,000 were claiming the extra milk allowance on the grounds of active tuberculosis, whilst the Survey of Sickness during the year ending April, 1947, yielded an average rate of 318 per 100,000 who said they had suffered from tuberculosis in a calendar month. Comparison with these estimates and with mass radiography statistics furnished by the Ministry of Health has not shaken my belief that notification statistics of respiratory tuberculosis, despite their acknowledged deficiencies, are capable of telling us many things we do not know and need to know about the epidemiology of the disease. In the present article it is possible only to dip into the notification data which are being analysed, and which it is intended to publish in detail.

NOTIFICATIONS COMPARED WITH OTHER DATA

Throughout the period 1922-39 the ratio of deaths from respiratory tuberculosis of persons who had been notified to the total notified people among whom they were calculated to have occurred remained remarkably constant at about 50 per cent. (Stocks and Lewis-Faning, 1944). From a later analysis of tuberculosis notifications during 1940-46 it was shown that the ratio, after increasing temporarily in 1940 and 1941, then decreased year by year to 40 per cent. in 1946, and the following comment was made (Stocks, 1949a, p. 13):—

> 'More people suffering from tuberculosis which is not proving fatal are being brought into the notification net, or else the fatality of the disease generally has fallen. The first explanation is more probably the true one, notification being more complete now than it was before the war'.

The record can now be carried to 1948, the figures for respiratory tuberculosis since 1924 being summarized as shown in table 1. The 'corresponding notifications' in the last column are taken as one-fifth of the sum of notifications in the same year as the deaths *plus* twice those in the preceding year *plus* those in the second and third years back.

TABLE 1

Years (* mean annual)	Number of formal notifications	Deaths of notified persons from tuberculosis	Ratio (per cent.) of deaths to corresponding notifications
1924–27*	55,132	27,500	50
1928–31*	50,809	26,200	50
1932–35*	43,433	23,232	50
1936–39*	37,944	20,306	51
1940	36,151	21,410	58
1941	39,499	20,761	56
1942	40,629	18,385	48
1943	42,410	18,807	47
1944	43,794	17,769	43
1945	42,166	17,602	41
1946	42,173	16,929	40
1947	43,159	17,541	41
1948	43,971	16,424	38

The ratio for 1949 is not yet known precisely but it seems likely that it was about 35 per cent. The annual notifications increased in the ten years between 1938 and 1948 from about 38 thousand to 44 thousand, whereas total annual deaths, including those of persons not notified, decreased, as will be seen, from about 21½ to 17½ thousand.

In the years 1944 onwards, increasing numbers of people with active pulmonary tuberculosis were found by the expanding mass radiography surveys, and if it be assumed that none of these had been or would have been notified without the surveys, and that all of them were notified, the maximum possible effect on the notification totals would have been as shown in table 2.

TABLE 2

Year	Number of notifications	Active cases found by surveys	Difference	Maximum fatality ratio (per cent.)
1944	43,794	2,900	42,500	43
1945	42,166		40,500	42
1946	42,173	2,523	39,650	41
1947	43,159	2,469	40,690	43
1948	43,971	3,388	40,583	41

The active cases included both primary and post-primary tuberculosis, and also pleurisy with effusion. The figures for 1944 and 1945 are approximate, and the corrected fatality ratios are calculated as explained for the

preceding table, using the numbers in the 'difference' column as minimal estimates of the numbers who would have been notified in the absence of mass radiography. The assumptions made are extreme ones and the resulting correction of the ratios must be excessive. It may be concluded that the fatality of notified persons has in reality fallen by about one-fifth compared with the period between the two wars, and that the apparent fall below 40 per cent. in 1948 and 1949 is probably accounted for by more complete notification resulting directly or indirectly from mass radiography.

There is a consistency between notification statistics and those obtained independently from other sources. In the study of survival of notified cases of respiratory tuberculosis in the years before the war (Stocks, 1944) it was estimated that the average interval between notification and death of the fatal cases was about 2.2 years, and the average duration of the active state after notification in the other half who survived was between two and three years. It is now possible to calculate the average total duration of 'activity' by comparing the proportions with active disease at various ages at a given moment according to the findings of mass radiography with the rates at which new cases arise according to notification statistics. In table 3 the mass radiography rates (R) are based on the totals examined during 1944-49, and the notification rates (N) are those of 1947 at the middle of that period. The ratios of the one to the other provide estimates of the duration of the 'active' state, in years, at different age periods for each sex.

TABLE 3

Age Period	Males				Females			
	Rates per 100,000		Ratio R/N	No. of notifications	Rates per 100,000		Ratio R/N	No. of notifications
	R	N			R	N		
15–	345	193	1.8	5,864	506	235	2.2	7,043
25–	375	163	2.3	5,307	472	146	3.2	4,855
35–	327	116	2.8	3,886	255	66	3.9	2,264
45–60	422	136*	3.1	5,000*	179	36*	5.0	1,550*

* Approximate figures

This suggests that the average duration was about two years at the ages of 15-25, increasing with advancing age to about three years for men at the ages of 45-60, and five years for women of those ages. Weighing the durations by the numbers notified, an average duration of 2.7 years for adults is indicated, and some increase since 1938 would not be surprising in view of the improved survival rate. If the notification rate at ages over 15 is multiplied by 2.7, this gives an estimated prevalence rate of active respiratory tuberculosis of 115 x 2.7 = 310 per 100,000, which agrees quite well with the measure for 1947 obtained from the Survey of Sickness, which has already been mentioned.

CHANGES IN NOTIFICATION AND DEATH RATES SINCE 1938

When notification and death rates for respiratory tuberculosis in 1948 are compared with those in 1938 at different age-groups, the increases and decreases per cent. of the 1938 rates were as shown in table 4.

TABLE 4

Age Group	Males		Females	
	Notifications	Deaths	Notifications	Deaths
0–	+120	−12	+156	+18
5–	+ 21	−65	+ 38	−33
15–	+ 27	−37	+ 38	−15
25–	+ 18	−18	+ 17	− 4
35–	− 14	−26	− 6	−21
45–	− 4	−15	− 19	−25
55–	+ 10	+ 7	− 17	−24
65+	+ 23	+33	− 11	−13
All ages	+ 8	−13	+ 12	−19

Among young children notification rates increased greatly without much change in death rates but, as will be seen in table 5, there was a sharp fall in deaths from 259 in 1947, to 198 in 1948, and comparison of 1947 with 1938 rates showed increases for both sexes. At the school ages, notification rates also increased although death rates were much lower than in 1938. Mortality of children from meningitis and other forms of tuberculosis was greatly reduced in the ten years, as shown by the rates at ages under 5 years. It seems probable that incidence of the respiratory form in children increased

TABLE 5

Form of tuberculosis	Number of deaths at ages 0–5 years				Rates per 100,000			
	Boys		Girls		Boys		Girls	
	1947	1948	1947	1948	1938	1948	1938	1948
Respiratory ..	139	105	120	93	6.4	5.6	4.4	5.2
Meningitis	389	335	315	295	29.7	17.9	30.0	16.6
Other	166	107	112	100	15.6	5.7	11.2	5.6

owing to a falling off in sanatorium isolation of adults, and that the fatality of the disease has been lowered in recent years. The actual numbers of notifications and deaths of children are too small, however, to have any appreciable effect on the total respiratory rates at all ages.

Among young adults between the ages of 15 and 35, notification rates increased in the ten years, whilst the death rates declined for each sex. At ages between 35 and 55 both rates fell, the death rates improving more than

the notification rates. Among men over 55 both rates increased, whereas among women over 55 both rates declined.

It may be concluded that among young adults cases of respiratory tuberculosis were being more completely notified in 1948 than was the case ten years before, but whether real incidence had increased at all at that important age period remains doubtful. The comparisons show that the ægrescence rate, that is the rate of appearance of new illness caused by active disease, if it improved at all, did not fall to the same extent as the death rate; and therefore either the recovery rate at this age period improved or else the average interval between notification and death was lengthened. Probably both of these occurred.

At ages around 50 for each sex there must have been real decreases both in ægrescence rates and in death rates; but after 55, men showed increases both in notifications and deaths, in strong contrast with women of the same ages, whose rates fell considerably. Since better ascertainment by skiagraphy, more complete notification and more accurate certification of the cause of death would affect both sexes, some factors must have been operating to the detriment of men in comparison with women at ages over 55. There can be little doubt that this is an example of the so-called 'generation' or 'cohort' effect on tuberculosis incidence and mortality, on which stress has been laid by several writers (Frost, 1939; Picken, 1940; McDougall, 1949; Springett, 1950). This means that tuberculosis rates in a given year at a particular age period are a function not only of conditions, climate, epidemic and economic, which prevailed in that year, but also of the conditions which the people who reached that age-group in the year had encountered during their lifetime, the reactions they had made to them, and also the selection brought about by deaths during that process. Men aged 58 in 1948, for example, were children during the last decade of the 19th century; many of them were exposed to the rigours of war service during 1914-18 and experienced then a considerable weeding out by death of large numbers of their most healthy members. They reached their forties during the economic depression with its high unemployment rates, and in their early fifties many had to undertake exhausting home defence services in the second world war. It is hardly surprising that they suffered higher sickness rates and death rates from respiratory tuberculosis in 1948 than did the cohort of men attaining the same age in 1938, who had not been exposed to such conditions in either war.

MORTALITY FROM DIFFERENT FORMS OF TUBERCULOSIS

In table 6 are shown the actual numbers of deaths from tuberculosis of the respiratory system, of the meninges and central nervous system, and of all other parts of the body at all ages, in each year from 1938 to 1949. In 1938 and 1939 there were about 21½ thousand deaths from respiratory tuberculosis, and in 1940 and 1941 the number rose sharply to about 23½ thousand

and fell back to about 21 thousand in each of the next two years. The wave of high mortality in 1940-41 was an example of the immediate effects on fatality of people with tuberculosis who were exposed temporarily to severe conditions of climate and of war; it affected people of every age and was distinct from 'generation' effects. The deaths in the table include those of non-civilians registered in England and Wales.

TABLE 6

Year	DEATHS FROM TUBERCULOSIS IN ENGLAND AND WALES					
	Respiratory		Meningitis		Other Tuberculosis	
	M	F	M	F	M	F
1938	12,445	8,837	918	873	1,343	1,123
1939	12,702	8,840	868	816	1,361	1,036
1940	13,920	9,740	957	929	1,424	1,174
1941	13,985	9,648	1,195	1,170	1,457	1,215
1942	12,511	8,478	1,023	972	1,403	1,162
1943	13,064	8,278	960	988	1,256	1,103
1944	12,226	7,878	942	899	1,168	1,050
1945	12,077	7,936	918	927	1,154	943
1946	11,753	7,612	832	798	995	857
1947	12,058	8,098	817	749	964	865
1948	11,591	7,497	656	665	844	730
1949	10,700	6,777	570	533	718	533

In 1944 the downward trend of respiratory tuberculosis deaths which had been in progress between the wars was resumed, with a decrease of some 1,200 deaths. Further improvements occurred in 1945 and 1946, but they were negatived by an increase in 1947 which brought the deaths back again to 20 thousand as in 1944. In 1948 a large decrease of 1,068 was recorded, followed in 1949 by a still larger fall of 1,611, reducing the annual total to 17½ thousand. During this time the population had been getting larger and the crude death rate of 516 per million in 1938 was down to 439 in 1948 and 399 in 1949 (rates including deaths of non-civilians at home and based on the total population inclusive of Armed Forces at home and abroad). The Comparative Mortality Index, which is a civilian index adjusted to allow for effects of changes in age structure of the population, based upon unit value in 1938, was 0.862 in 1948, indicating a decrease of 14 per cent. in the ten years. For males only it was 0.866, and for females 0.849, the decline being rather greater for females than for males.

Deaths from tuberculosis of the meninges and central nervous system increased to a maximum in 1941 and then began to fall, but in 1945 they were no fewer than in 1938. A rapid decline then occurred, reducing the total from 1,845 to only 1,103 in 1949. For other non-respiratory tuberculosis also a peak level was reached in 1941, the normal downward trend being resumed after 1942, with the result that by 1949 the deaths numbered only

half the total of ten years earlier. It may be presumed that increasing pasteurization of milk has contributed to the recent rapid fall, which has been more pronounced among females than males.

A recent study by the Medical Research Council (1949) showed that the percentages of patients whose infection was of bovine type, giving equal weight to the various regions of England, were: cervical glands 46, abdominal tuberculosis 36, meningitis 27, genito-urinary 13, bones and joints 11. For all non-pulmonary tuberculosis combined the proportion was 39 per cent. among children under 5; 44 per cent. at 5-10; 35 per cent. at 10-15; and 13 per cent. at ages over 15; and at all ages it was 22 per cent. among males, and 27 among females.

It is of interest to compare the changes in the notification and death rates since 1938 in England and Wales with those in the United States of America for *all* forms of tuberculosis combined (table 7). The death rate in the U.S.A.

TABLE 7

	Rates per 100,000					
	England and Wales			U.S.A.*		
	1938	1947	1948	1938	1947	1948
New cases notified or registered	123	120	121	82	93	100
Deaths of unnotified persons ..	7	9	8	—	—	—
Total deaths	62	55	51	49	34	30
Ratio of new cases to deaths ..	2.0	2.2	2.4	1.7	2.7	3.3

* Based on figures given by Edwards and Drolet (1950), rates for 1948 being provisional estimates.

decreased more rapidly and the registration rate of new cases increased considerably, raising the ratio of cases to deaths to 3.3, compared with 2.4 in England and Wales. The death rates of white male and female adults per 100,000 at different ages in the United States for the years 1939-41 and 1948 are compared in table 8 (Fish and Spendlove, 1950).

TABLE 8

	15–	20–	25–	30–	35–	45–	55–	65–	75–	85+
Males:										
1939–41 ..	11	24	35	44	58	84	100	101	89	73
1948 ..	4	10	15	23	37	64	86	104	104	101
Females:										
1939–41 ..	19	37	43	39	33	29	38	55	70	55
1948 ..	6	15	18	18	19	16	21	38	50	60

NOTIFICATION AND DEATH RATES IN TOWNS AND COUNTIES

Comparison of relative proportionate mortality at two age-periods, 15-45 and 45-65, based on total deaths at those ages from all non-violent causes,

has been made between the periods 1932-36 and 1942-46 for each of the regions (Stocks, 1949b). It was estimated that Wales and the North-East of England had the highest mortality from respiratory tuberculosis among young adults and women aged 45-65, whilst the West Riding of Yorkshire was remarkable for its low mortality in those groups. On the other hand the regions with highest death rate of men aged 45-65 appeared to be Greater London and Lancashire. The Registrar-General's estimates of populations by sex and age at the end of 1947 have now made it possible to obtain mean annual notification and death rates in the two-year period 1947-48 for different regions and counties at various ages. A convenient method of comparison is to calculate equivalent average rates at the ages of 15-45 by taking one-sixth of the sum of the rates for males and females aged 15-25, plus one-third of the sum of the rates for males and females aged 25-45. The resulting rates of notification (E.A.N.R.) and death (E.A.D.R.) are therefore standardized to a population uniformly distributed between ages 15 and 45. Full details of the numbers of notifications and deaths will be published in due course in the Registrar-General's reports, and only a few rates can be given here.

The trend between 1938 and 1948 of crude notification rates of respiratory tuberculosis at all ages in several of the large cities is shown in table 9, remarkable contrasts being apparent:—

TABLE 9

NOTIFICATION RATES PER 100,000 LIVING AT ALL AGES IN ALTERNATE YEARS

	1938	1940	1942	1944	1946	1948
England and Wales	92	86	97	103	99	101
London County	128	134	180	183	154	161
All County Boroughs	110	104	116	120	117	119
Birmingham	97	86	102	107	104	101
Liverpool	167	166	187	193	192	202
Manchester	124	145	136	122	114	123
Leeds	103	114	126	125	93	89
Newcastle-on-Tyne	153	159	168	168	192	181
Rest of England and Wales ..	75	71	79	86	82	84

The London rate rose to a high level during the war years, and in 1948 it was still 26 per cent. above that of 1938. The county borough rate showed only a moderate increase, amounting to 9 per cent. in 1944 and 8 per cent. in 1948. Liverpool's rate rose progressively, however, to a level 21 per cent. higher in 1948 than in 1938, whilst Newcastle's rate rose sharply after the war. Manchester's rate returned to pre-war level after 1947, and that of Leeds fell below the pre-war figure after 1944.

Northern counties.—In table 10 those northern counties, including county boroughs within their boundaries, where there were at least 400 notifications

at ages 15-45 in the two years 1947-48, are arranged in descending order of their equivalent average notification rates as defined above (E.A.N.R.); and the death rates (E.A.D.R.) and deaths per 100 notifications, all at ages 15-45 in 1947-48, are also shown. The agreement between notification and death rates in these counties was very close, the ratio of deaths to notifications varying very little from 45 per cent. Cumberland and Westmorland together had 384 notifications and 186 deaths at the ages of 15-45, producing a ratio of 48 per cent.

TABLE 10

	Notifications at 15–45 in 1947-48	E.A.N.R. per 100,000	E.A.D.R. per 100,000	Deaths per 100 notifications
Northumberland ..	1,320	200	87	45
Durham	2,314	185	85	46
Lancashire	6,686	161	66	43
Yorks.: N. Riding ..	619	150	62	42
Yorks.: E. Riding ..	587	144	63	45
Yorks.: W. Riding ..	3,645	125	52	44
Cheshire	1,205	125	50	43

For four of the counties it is possible also to compare the ranking according to notification rates with the ranking according to frequency of active tuberculosis found in mass radiography surveys carried out in towns within those counties during 1944-49. From the aggregated figures for the whole of England and Wales obtained by the Ministry of Health from the surveys from October 1943, to the end of 1949, rates of frequency of active tuberculosis (including active primary, post-primary and pleural effusion) were calculated for each sex at ages 14, 15-24, 25-34, 35-44, 45-59, 60 and over. These 'standard rates', based on over four million examinations, were then applied to the age distributions of all the people examined within a particular county, giving the 'expected' number of active tuberculosis cases, and the ratio of the actual number found to the expected number gives a comparative radiography index (C.R.I.) for that county. The selection of persons examined apart from sex and age, may have been affected by all sorts of factors, as may also the final assessments of diagnosis, but nevertheless, this comparative index corrects for differences in sex and age selection and provides an approximate measure of relative, although not of absolute, prevalence of active respiratory tuberculosis at the 'working' ages of life.

The values of the C.R.I. were: Northumberland 2.37, Durham 1.94, Lancashire 1.45, and the West Riding of Yorkshire 0.67. The order was the same as for the notification rates and the death rates at ages 15-45, the contrasts, however, being for some reason greater. The general conclusion is that in the northern counties of England the notification rates of respiratory tuberculosis at ages 15-45 are consistent with other indices, and may be used

with some confidence as relative measures of the occurrence of new active cases which satisfy the criterion of 'suffering from' the disease as generally interpreted. This is not to deny that some proportion of such young adults are escaping notification in the north, but the proportion must be small and not so variable as to destroy the value of notification statistics.

Midland counties.—In table 11 are compared the young adult rates in 1947-48 of six midland counties including county boroughs, and also of Oxfordshire.

TABLE 11

County	Notifications at 15–45 in 1947–48	E.A.N.R. per 100,000	E.A.D.R. per 100,000	Deaths per 100 notifications
Nottingham	1,328	195	65	35
Warwick	2,465	161	65	43
Stafford	2,040	149	62	43
Leicester	753	147	60	43
Northants	376	138	46	35
Oxford	319	134	46	34
Derby	666	97	37	40

Here the contiguous counties of Warwick, Stafford, Leicester and Derby show close correspondence between notification and death rates and a ratio of deaths to notifications only slightly below that in the northern counties. Nottingham, Northampton and Oxford also agree among themselves in ranking according to the two rates, but had a distinctly lower ratio of deaths to notifications than the other group. The comparative radiography indices of four of the counties were: Nottingham 1.17, Stafford 0.97, Northants 0.81, Warwick 0.73, the ranking of the first three agreeing with that of the notification rates, although that of Warwickshire did not. This suggests that the low ratio of deaths to notifications in Northants was not due to more complete notification, and it is reasonable to conclude that in that county and Oxfordshire, which are largely agricultural, the real fatality of respiratory tuberculosis may be less than in the industrial midlands. Nottingham's notification rate was high, even in comparison with its death rate and C.R.I., and possibly notification was unusually complete in that county.

Southern counties.—In the south-west part of England, Dorset, Devon and Cornwall gave rather high ratios of deaths to notifications among young adults: 40, 44 and 48 per cent. respectively; but this might well be due to tuberculous invalids moving into those counties on account of the favourable climate, and some of them dying there. Worcestershire also gave a high ratio of 50 per cent., which is difficult to explain otherwise than by incomplete notification.

The notification statistics of London and the neighbouring counties are

complicated by many factors such as the inward movement of young adults from Wales, Ireland and rural areas to London, where the outcome of exposure to infection may be notification within the London area followed by return to their original home areas, where some die. As for other infectious diseases, there is also probably a greater tendency in and around London to notify doubtful cases. These things tend to inflate the notification rates in London and Middlesex particularly, and to produce ratios of deaths to notifications which underestimate the real fatality (table 12).

TABLE 12

County	Notifications at 15–45 in 1947–48	E.A.N.R. per 100,000	E.A.D.R. per 100,000	Deaths per 100 notifications
London	7,290	250	63	27
Middlesex	3,873	207	43	23
Kent	2,026	175	56	34
Essex	2,696	165	49	31
Surrey	1,909	155	40	29

Mass radiography statistics for these counties are confused by the fact that they are mostly related to place of work rather than of residence; but when the data for London, Middlesex, Essex and Surrey were aggregated, the C.R.I. was 0.82, similar to indices found in the midlands. Allowing a 25 per cent. inflation of London and Middlesex notifications of young adults, the ratios of deaths to notifications in the South-East seem to indicate a survival rate of about two-thirds among young adults who are notified, compared with about one-half for those residing in the north of England.

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SOME REFLECTIONS ON MASS MINIATURE RADIOGRAPHY

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It is now seven years since the introduction of mass miniature radiography into civilian practice in this country, so that sufficient experience has been gained of its work to allow of at least a preliminary assessment of its value, and in the light of this to consider its future. It is not proposed in this article to deal in any detail with cardiovascular diseases, but to concentrate on pulmonary conditions, more especially tuberculosis.

THE NECESSITY FOR MASS MINIATURE RADIOGRAPHY

For years the clarion cry of those working in the tuberculosis service has been 'better ascertainment with earlier diagnosis', and until recently this cry has almost been unanswered. That such a cry was justified is shown by the fact that in Wales in the year 1939, of every five definite cases of pulmonary tuberculosis seen for the first time at the clinics, only one was in the early and essentially curable stage of the disease, whilst two were intermediate and two advancde. The result of this delayed ascertainment was that nearly half of those diagnosed that year died within twelve months of first examination. Figures for England and Scotland differed hardly at all.

It was unfair and futile to blame either the patient or the general practitioner for this unhappy state of affairs, for active pulmonary tuberculosis can exist for months or even years without any symptoms; often when symptoms are present they are so varied or indefinite as not to focus attention on their real cause, and by the time abnormal physical signs are found in the chest the disease has ceased to be in its early stage. Further, if the patient did consult his doctor it was impossible for all those with vague symptoms to be referred to the chest clinics, for these were more often than not ill-equipped to deal with such large numbers.

The aim of mass radiography is essentially the prevention of disease through the discovery of possible sources of tuberculous infection, and is therefore twofold. There is, however, a danger that the medical directors of units may lose sight of the preventive aspect of approach in their selection of groups to be surveyed, for now they are allied through the regional hospital boards with the diagnostic machine, and separated from the public health authorities. The solution surely is that they should be partly employed in chest clinics which, although controlled by the hospital boards, are fortunately still linked to local health departments and therefore maintain interest in preventive medicine. This arrangement would have the added advantage of widening their clinical experience as well as affording the

opportunity of personally following up the cases discovered in their units.

The appeal of a mass miniature radiography unit is obvious, in its mobility, in the amount of work it can do in a day, in its comparative cheapness after the initial outlay and, most important of all, in the fact that those with tuberculosis can now be searched for among the apparently healthy at their place of work. But it must be remembered that it acts only as a filter or screen of abnormal pulmonary or cardiovascular shadows, and that the diagnosis and significance of these are decided after clinical, full-sized radiographical, and other examinations are carried out in a chest clinic or general hospital; for radiology alone can suggest but never establish a diagnosis in chest disease.

THE VALUE OF THE MINIATURE FILM

The 35 millimetre film is in general use for mass radiography in this country, and the question of its reliability compared with the standard 15 inch x 12 inch film arises. Does it miss a significant number of abnormal shadows? Is it of the same diagnostic value when these shadows are seen? Experience shows that it is not quite so reliable in either capacity; this is not surprising, for it is obvious that there must be some loss of shadow definition in fluorescent screen photography compared with direct-contact radiography, and a further loss by the necessity of film projection for viewing and interpretation. The localized lesion is rarely missed, but, for example, the fine reticulation or the very early generalized nodular opacities of silicosis may be overlooked. Further, units are often forced to work at great speed, and then naturally there is a fall-off in the *perfect quality* film which is so essential if mistakes are to be avoided. It is difficult to decide who should read the films. Nearly all the medical directors of mass radiography units are experienced mainly in pulmonary disease, and have little, if any, specialized knowledge of cardiovascular conditions, so that the ideal would probably be a team composed of a chest physician, a cardiologist, and a radiologist to maintain a proper balance.

THE PRESENT SCOPE OF MASS MINIATURE RADIOGRAPHY

Until sufficient units become available it is wise to concentrate the activities of those we have on sections of the population which are thought to be especially susceptible to serious respiratory diseases, and not to carry out haphazard surveys. Examination of school children below the age of fifteen is a misdirection of effort, for pulmonary tuberculosis is relatively uncommon among them as is shown by the fact that in Wales, of nearly 35,000 children surveyed only seven cases were found, whereas of every thousand adults examined nearly four had previously unsuspected tuberculosis.

Some population groups that should be productive in case finding or in which there is some other reason for examination will now be considered:—

(a) In females there is a high incidence of tuberculosis in young adult

life. This suggests the survey of the personnel in industries and large offices which employ mainly young women.

(b) Although it is correct to say that pulmonary tuberculosis is a comparatively rare disease in children, it is beyond doubt that uncontrolled infection at this time of life, and especially in older children, often leads to progressive disease in adolescence, and therefore local health and education departments should be persuaded to encourage those whose occupations are related to children to have a periodic X-ray examination.

(c) It is probably now true to say that the incidence of tuberculosis in the great majority of the main occupational groups (Registrar-General's classification) is little affected by the nature of the work, but there are certain occupations where the workers are exposed to silica dust or where there is close contact with infection, as occurs with nurses and medical students, and these are especially prone to tuberculosis and should have serial chest X-rays. Again, pneumoconiosis is still far too common, notably in South Wales, and periodic survey of those in dusty occupations should add to the knowledge of the development and prevention of this disease.

(d) It is almost unnecessary to stress the importance of tuberculosis in the military services, especially in war time, for, disregarding the humanitarian aspect, this disease alone has cost the country a vast sum of money in treatment and pensions. That all recruits and, where possible, all military personnel, should be subjected to chest radiography is now generally accepted.

(e) There are certain population groups made up of a fairly large number of people segregated together in close contact for long periods, and where a case of active tuberculosis can be a potent danger; examples of these are young girls living in hostels, and patients in mental hospitals. Here the discovery and removal of the source of infection can do much to reduce the high incidence of the disease in these groups.

So far no mention has been made of household contacts to tuberculosis. That these would be a fertile source in case finding is shown by the fact that tuberculosis is about five times as common in them as in the general population. But for this very reason, and often through continued contact, it is essential that clinical and radiological examination, with tuberculin testing, be carried out at frequent intervals, say, three to four times a year. It is obvious that mobile radiography units are, through their inaccessibility, unsuited for this purpose, and it is better to leave contact examination to the chest clinics.

SOME DEFECTS OF THE SCHEME

With further expansion of the service, a time should come when it is possible to offer a periodic chest X-ray examination to the whole adult population, but until this time arrives it is unwise and a dissipation of effort to carry out public surveys in towns and villages. Lack of periodic examination is one of the greatest dangers of mass miniature radiography, for pulmonary tuberculosis may develop in a matter of months, and there is then the risk

of the patient being lulled into a feeling of false security by a negative report some time before the development of symptoms which would normally have induced him to see his doctor. The ideal is a chest X-ray examination at about *yearly* intervals, but this will entail an enormous number of units and personnel, and a very high cost.

Another danger arises from the fact that the examination is voluntary, for any coercion would quite rightly be resented by the general public. With intensive and well-organized propaganda, however, the percentage of volunteers from factory and office is in the region of seventy to eighty, whereas for the public surveys it is only about twenty. It is essential that the propaganda be honest ; for example, to suggest, as has been done, that a miniature X-ray film detects early heart disease is misleading, and unfair to the patient, and tends to bring the service into disrepute. The chief reason for refusing to be examined is fear of what may be found, and this is naturally more noticeable in those with symptoms or a family history of tuberculosis. It is therefore fairly certain that the incidence of chest disease is much greater among refusals than in volunteers, but so far this has not been proved. This dangerous reservoir of non-cooperators constitutes a difficult problem, but nothing, apart from persuasion, can be done about it.

MASS MINIATURE RADIOGRAPHY SURVEYS

According to the report of the Ministry of Health for the year ended March 31, 1949, nearly three million persons had been examined by mass miniature radiography by the end of 1948. Of these, the great majority (94.4 per cent.) had no radiographical chest abnormality, but 0.4 per cent., or slightly over 11,000 people, were found to have previously unsuspected active pulmonary tuberculosis, and 2.3 per cent., or about 65,000 persons, had inactive lesions or required further observation at the chest clinics. 405 patients with malignant disease of the chest were discovered, and over 13,000 cases of cardiovascular disease noted, but it is certain that many of the latter were already known about. Let it be said straight away that the finding of so many cases of active tuberculosis in those who were apparently in good health, more than justifies from the public health point of view alone, the labour and expense of the scheme, for they would cease to be a danger to their fellow-workers, and much less of a danger at home through education in how to avoid the spread of infection. Further, from the individual point of view it is reasonable to expect that the prognosis of the disease would, generally speaking, be good, in that the diagnosis had been obtained before symptoms and ill-health had appeared. This raises the question of to what extent mass radiography cases are discovered in the early stage of the disease compared with the routine new cases; to answer this the classification of those in each of these groups in Wales is shown in table 1.

It is seen from this table that the percentage (47.0) of early cases discovered by mass radiography is a big improvement on that (29.5) for routine

cases. It should be remembered that all the mass radiography suspects had eventually to pass through the same diagnostic machine as the routine new cases, therefore the criteria for the classification and assessment of activity would be the same for both groups.

In England and Wales, for the period 1943-48, over 250,000 persons were notified as suffering from pulmonary tuberculosis, and of these only

TABLE 1

Showing the stage of tuberculosis in cases discovered by mass radiography in Wales (1944-49) and at the chest clinics in Wales for the year 1948 (percentages in brackets).

Mode of Discovery	Number	Stage of the Disease		
		Early	Intermediate	Advanced
M.M.R.	783	368 (47.0)	319 (40.7)	96 (12.3)
Clinics	2721	802 (29.5)	1199 (44.0)	720 (26.5)

about 11,000 had been discovered by mass miniature radiography, so it is obvious that the latter can have only slightly influenced the picture as a whole in regard to early diagnosis. That this is so is, of course, due to the limited development of miniature radiography, and each year, as the service has expanded, its effect must have been greater.

Apart from any influence of mass radiography the diagnostic picture has much improved, so that in Wales last year the proportion of early cases was greater than that of advanced, and the credit for this must go to the greater use of chest clinics through a more enlightened attitude of the medical profession and the general public. Now that this improvement has been accomplished, is it worth while expanding the mass radiography service? The prognosis and infecting danger of early and advanced tuberculosis differ so much that surely every factor that can lead, even in a small way, to the detection of the disease in a curable stage should be developed to the full, with, of course, the proviso that it is most important not to over-emphasize any one of the factors concerned in an anti-tuberculosis scheme, for it is only by due regard to the principles of prevention, diagnosis and treatment, including rehabilitation, that ultimate success will be assured.

If, as time goes on, more and more units become available, the ideal of serial chest radiography of the adult population will eventually be reached. When this becomes possible, much new and valuable information will be gathered about certain epidemiological aspects of tuberculosis, the incidence of the disease in the whole adult community, and in selected groups, so that the influence on it of age, sex, occupation, and conditions of life can be studied further. With the discovery of many minimal and latent lesions, and their follow-up, much new knowledge will be acquired as to their nature, whereby the important can be separated from the unimportant. From the community point of view, mass miniature radiography as it grows

will be of great educational value for the preservation of good health.

AN ADAPTATION OF MASS MINIATURE RADIOGRAPHY

Early in 1948, a further application of the principle of mass miniature radiography was introduced at the Cardiff chest clinic by the linking of a fluorographic unit to the existing X-ray plant, so that 35 millimetre films could be taken. Special sessions were arranged to which the local practitioners were invited to send patients with symptoms of ill-health only *vaguely suggestive* of pulmonary tuberculosis. Those attending these sessions are X-rayed only, neither history taking nor physical examination being carried out, but when a pulmonary abnormality is found the patient is recalled for full investigation, and if cardiovascular disease is suspected the family doctor is informed so that he may take whatever action is necessary. If more definite symptoms of tuberculosis are present, the patients are referred to the clinic in the usual way for clinical and other examinations. The aim of this scheme is primarily to reduce these routine new patients, and at the same time to give an easily available chest X-ray service to the medical practitioners, so that more, and possibly earlier, cases of tuberculosis, as well as other diseases, may be discovered. Nearly every chest clinic in this country is so overworked with routine new patients, the great majority of whom have no chest disease, that little time is left for the vitally important function of guiding those with tuberculosis in their medical, social and economic problems. It is recognized that this service can not help in the diagnosis of certain diseases like bronchitis, asthma and early bronchiectasis, in which clinical examination is of more value, but this defect is greatly outweighed by the discovery of many more serious conditions.

This static miniature radiography unit quickly became a success, and in its second year of work 5000 people were referred to it from a population of 320,000; of these 64 (1.3 per cent.) were found to have previously unsuspected tuberculosis, and 83 (1.7 per cent.) required further observation. The percentage of cases of pulmonary tuberculosis discovered is about three times greater than that for mass surveys of presumably healthy people, but this is not surprising, for those examined by the static unit had some symptoms of ill-health. A danger of this scheme that early became apparent was the reference of patients who required prolonged observation, for example contacts, and cases of pleurisy or erythema nodosum; but the practitioners readily responded to a request to send these to the routine sessions and not to this unit.

So far this use of miniature radiography has stemmed what had been an ever-growing stream of routine new patients and, if further experience confirms its value, the future should see its adoption in densely populated areas. It is not, however, suggested that this type of miniature radiography unit should compete in the carrying out of surveys of the apparently healthy, for this is better performed by mobile units, or in a building that is not, in the public mind, associated with disease.

THE CHEMOTHERAPY OF TUBERCULOSIS

By JOHN CROFTON, M.D., M.R.C.P.

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In the chemotherapy of tuberculosis the following drugs are the only ones which have come into current clinical use:—

(1) Streptomycin
(2) Dihydrostreptomycin
(3) *Para*-aminosalicylic acid (P.A.S.)
(4) The sulphones
(5) The thiosemicarbazones.

STREPTOMYCIN

Pharmacology.—Streptomycin is an antibiotic derived from a soil fungus, *Streptomyces griseus*. It is supplied either as the hydrochloride, the sulphate, or as the calcium chloride double salt. It is readily soluble in water. In sealed ampoules the powder is stable at room temperature for many months, and even in solution there is no loss of potency for two months or more. In adult tuberculosis the usual dose is 1 g. a day, which is now commonly given in a single intramuscular injection. But in severe cases of tuberculous meningitis or miliary tuberculosis, and possibly in genito-urinary tuberculosis, it may be advisable to give 2 g. a day in two doses of 1 g. Children may be given 0.02 g. per pound body weight per day. For intrathecal injection, 0.05 to 0.1 g. should be given dissolved in at least 5 ml. of saline, and the solution mixed with cerebrospinal fluid during injection; for children under three, a dose of 0.05 g. should not be exceeded.

Drug resistance.—The most important disadvantage of streptomycin is that in a high proportion of cases of pulmonary tuberculosis treated with the drug the tubercle bacilli become resistant to its action. Once they become resistant they usually remain so permanently. The resistant bacilli emerge sometimes after only two or three weeks' treatment, more commonly after six weeks or more. Within a few weeks of first detection the majority of the patients' bacilli will have become resistant, and streptomycin will then be of no further value in treatment. Patients carrying resistant tubercle bacilli may infect others; the disease in the new patient will be no different except that it will be unaffected by streptomycin. Cases of such transmission have already occurred, and it is an important argument against using streptomycin except when it is clearly indicated. In genito-urinary tuberculosis the organisms also become streptomycin-resistant in a high proportion of treated cases unless the urine is permanently cleared of tubercle bacilli. But in miliary tuberculosis and in tuberculous meningitis resistant bacilli are less common.

Preliminary trials both in this country and in the United States of America have shown that there is an impressive reduction in the incidence of streptomycin-resistant tubercle bacilli if *para*-aminosalicylic acid (P.A.S.) in adequate doses is given at the same time as the streptomycin. These results make it no longer justifiable to give streptomycin without P.A.S., certainly in pulmonary and genito-urinary tuberculosis, and probably in other types. But until the risk of resistant bacilli emerging has been more accurately assessed it is wise to assume, in planning treatment of pulmonary or genito-urinary tuberculosis, that the patient's bacilli may become resistant.

Toxicity.—The second main disadvantage of streptomycin is its effect on the vestibular apparatus. This occurs in a high proportion of cases on 2 g. streptomycin a day; in a lower, but still significant, proportion on 1 g. a day. The main symptom is giddiness, which usually comes on between the third and the seventh week of treatment. In many cases it lasts only a few days or a few weeks, but in some, especially the elderly, it may last for many months. At the same time as the giddiness develops, the caloric tests show a diminution or absence of the normal nystagmus which occurs when hot or cold water is run into the external auditory meatus. Some cases do not complain of giddiness but are found to have lost their caloric responses. On close questioning they will often admit unsteadiness in the dark or on sudden turning. It seems possible that in certain severe cases these changes will be permanent. Nevertheless, if streptomycin is used in the proper cases, namely, those in which it is part of a programme designed to save a patient's life, it is justifiable to ignore the effect on the vestibular apparatus and to continue treatment, even though giddiness develops.

Urticarial and other rashes may occur, usually within the first three weeks of starting treatment. They may be treated with antihistamine drugs (phenergan, 50 mg., every night; anthisan, 100 mg., three times a day; or antistin, 100 mg., three times a day), but usually subside within a few days even if streptomycin is continued. Rarely, severe pyrexial reactions or true exfoliative dermatitis may occur. In such cases the drug will have to be stopped; but if it is important to give it, it may be possible to start treatment again beginning with 50 *micro*grammes, and working up by daily increments to the full dose. The early stages of desensitization may well be covered with antihistamine drugs given in the doses suggested above. Alternatively, dihydrostreptomycin may be tried, as patients sensitive to streptomycin are not always sensitive to dihydrostreptomycin. Nurses handling streptomycin may become sensitized. After weeks or months of exposure they may develop a rash on the hands, the flexures of the elbows or round the eyes. Handlers of streptomycin should always put on rubber gloves before opening the containers. They should wash the gloves after finishing cleaning the syringes, and wash their hands thoroughly after the gloves have been removed.

Using a dose of 1 g. of streptomycin a day, nausea and vomiting are rare.

If troublesome, these symptoms may be treated effectively with antihistamine drugs. Eosinophilia may occur, but is unimportant. With high concentrations in the urine, streptomycin may act as a reducing agent and simulate glycosuria.

CLINICAL APPLICATION OF STREPTOMYCIN

Miliary tuberculosis.—With intramuscular streptomycin treatment complete recovery can now be expected in over 50 per cent. of cases. Treatment should be continued for at least six months. The main cause of failure is the development of tuberculous meningitis. This should be watched for by regular examination of the cerebrospinal fluid, and intrathecal treatment should be started if there are any suggestive findings.

Tuberculous meningitis.—With streptomycin treatment the survival rate in most series is 20 to 30 per cent., but both intramuscular and intrathecal treatment is essential, and treatment must be continued for six months or more. Considerable medical and nursing skill is required, and treatment is preferably carried out in special centres.

Pulmonary tuberculosis.—Streptomycin is mainly effective in the exudative type of the disease, especially when this is recent. It is useless in chronic fibro-caseous disease, and tuberculous cavities are seldom closed. Further limitations are imposed by the possible emergence of streptomycin-resistant tubercle bacilli and by the toxic effects on the vestibular apparatus. It is therefore recommended that at present streptomycin should be used only in cases in which the disease is too acute or too extensive for collapse therapy, with the idea of achieving sufficient improvement for collapse therapy to be relatively safe. Streptomycin, accompanied of course by P.A.S., should only be given as part of a programme of treatment and should be continued until the patient is rendered fit for collapse therapy, whether this be a matter of weeks or months. The collapse should be instituted while the patient is actually under treatment with streptomycin or immediately afterwards. It is most dangerous to finish a course of streptomycin and leave the patient with unclosed cavities; he is likely to relapse within a short time.

Primary tuberculosis.—It is useless to use streptomycin in primary tuberculosis. There is no evidence that it has any effect whatsoever on this condition.

Tuberculous empyema.—Up to date, results with streptomycin in tuberculous empyema have been disappointing.

Tuberculous laryngitis and *tuberculous tracheo-bronchitis* respond well to treatment if the lesion is relatively recent and the lung disease slight or well controlled. In advanced tuberculosis with severe symptoms from laryngitis, it may be justifiable to give a short course of streptomycin for three weeks or so, as the symptoms are often temporarily relieved. In both conditions the lesions may heal, leaving troublesome residual fibrous stenosis.

Tuberculous ulcers of the mouth, tongue and pharynx, and *tuberculous enteritis* usually respond dramatically to streptomycin.

Tuberculous peritonitis.—The results in this condition are difficult to assess owing to the tendency to spontaneous improvement. Streptomycin is probably of value.

Chest surgery in tuberculosis.—The low incidence of spread of disease after thoracoplasty make it unjustifiable to use streptomycin as a routine cover for the operation, but if a spread occurs it usually responds well. On the other hand, streptomycin should definitely be given to cover resections for pulmonary tuberculosis. Tuberculous infection of the extrapleural space after thoracoplasty responds well to local and intramuscular streptomycin.

Tuberculous sinuses usually heal in one to four months with intramuscular streptomycin. Surgical measures should be taken to deal with pus, necrotic tissue or dead bone.

Genito-urinary tuberculosis is discussed elsewhere in this issue and will not be dealt with here.

Tuberculosis of bones and joints.—Although not dramatic, streptomycin probably has some effect and may be useful in making a number of cases fit for operation which would not otherwise become so.

Tuberculous lymphadenitis.—Many cases improve under streptomycin, but some fail to do so. When the glands have broken down, streptomycin, if used, should be combined with surgery.

DIHYDROSTREPTOMYCIN

This drug is derived from streptomycin by treating the latter with hydrogen and a catalyst. It is undoubtedly less toxic than streptomycin on the vestibular apparatus but more so on the acoustic apparatus. Deafness has been reported during or after treatment. Its somewhat lesser toxicity is counterbalanced by the conclusion that it is less effective therapeutically. Tubercle bacilli resistant to streptomycin are also resistant to dihydrostreptomycin, and resistant tubercle bacilli are just as liable to emerge in patients under treatment with dihydrostreptomycin. Its further use will probably be confined to cases developing severe reactions with streptomycin.

PARA-AMINOSALICYLIC ACID

Pharmacology.—*Para*-aminosalicylic acid (P.A.S.) is now generally supplied as the sodium salt. It is given by the mouth as a 20 per cent. solution in tap water. It has an unpleasant taste, like that of salicylates, which it is difficult to disguise. Patients usually prefer the unflavoured solution. The recommended dose is 5 g., four times a day. For children the dose can be calculated according to any of the usual formulæ. Coated granules of P.A.S. are available, but the amount required for each dose is too large for convenience. P.A.S., 5 g. four times a day, when given in conjunction with streptomycin in pulmonary tuberculosis, is known to result in a great diminution in the

proportion of cases in which streptomycin-resistant tubercle bacilli emerge. Whether smaller doses will suffice is uncertain; incomplete evidence suggests that less than 20 g. a day may prove less effective.

Drug resistance.—A number of cases of pulmonary tuberculosis have now been reported in which P.A.S.-resistant bacilli have emerged. Resistant bacilli have not often been reported in cases treated for less than three months, and there has been no report of P.A.S.-resistant bacilli when P.A.S. has been combined with streptomycin. If a patient whose sputum contains P.A.S.-resistant tubercle bacilli is treated with streptomycin, the bacilli may become resistant to both streptomycin and P.A.S. In consequence, streptomycin and P.A.S. should only be given together.

Toxicity.—Nausea and vomiting are common in patients taking P.A.S. but can often be avoided by giving the dose at the end of a meal. In severe cases the dose may have to be reduced or the drug temporarily stopped. Diarrhœa is not uncommon and is best treated with a chalk and opium mixture. Rashes may develop, usually in the first week or two of treatment, and may be treated with antihistamine drugs. Mild rashes may clear up even if P.A.S. is continued. If the rash is severe, or if there is fever, the drug may have to be stopped.

Clinical application.—In general, P.A.S. is a less potent drug than streptomycin. Miliary and meningeal tuberculosis are unaffected. Improvement in pulmonary tuberculosis is slower and less dramatic than with streptomycin, but, as with streptomycin, recent active disease responds best. Benefit has been claimed in most other forms of tuberculosis, especially in tuberculous enteritis, but in general the effects are less than with streptomycin. Tuberculous empyema has been treated with P.A.S. by local instillation of 20 ml. of 20 per cent. solution, once or twice a week. It is not yet established whether or not this treatment is of real value.

If streptomycin is for any reason contraindicated, it may be justifiable to give P.A.S. alone, preferably in courses of three months or less; but in general, both streptomycin and P.A.S. are best given together in order to avoid so far as possible the emergence of tubercle bacilli resistant to either drug.

THE SULPHONES

The sulphones are related to the sulphonamides. The active principle of the various sulphone preparations is diaminodiphenylsulphone, more simply known as D.D.S. Sulphetrone and promizole are the derivatives most used recently. These are broken down to D.D.S. in the body, and it is this substance which is probably responsible for both the therapeutic and the toxic effects. All the sulphones mentioned can be given by mouth. In general, no adequate evidence has yet been brought forward to justify the use of the sulphones alone in the chemotherapy of tuberculosis. In conjunction with streptomycin the little evidence so far available suggests that the

sulphones are less effective than P.A.S. in preventing the emergence of streptomycin-resistant tubercle bacilli. Excellent results have been claimed from combining promizole with streptomycin in the treatment of tuberculous meningitis, but further confirmatory work is required. The sulphones have definite toxic effects. Headache, nausea, vomiting, cyanosis, anæmia, rashes and thyroid enlargement have all been reported.

THE THIOSEMICARBAZONES

The thiosemicarbazones were introduced as chemotherapeutic agents for the treatment of tuberculosis by Domagk in Germany in 1946. The most active of the group was found to be 4-acetylaminobenzaldehyde thiosemicarbazone, also known as TBI-698 and commercially as 'contebin' in Germany, and as 'thioparamizone' in Great Britain. The drug has been extensively used in Germany but experience elsewhere is limited. Like P.A.S., it is taken by the mouth, and it seems probable that the clinical effect will prove to be similar. It is not yet known whether the combination of benzaldehyde thiosemicarbazone with streptomycin will prevent the emergence of streptomycin-resistant tubercle bacilli. It is already clear that the toxic effects are far from negligible. Nausea and vomiting, rashes, conjunctivitis, hæmolytic anæmia, agranulocytosis and liver damage have been described. It is too early to say whether benzaldehyde thiosemicarbazone will prove of practical value. Certainly its general use cannot yet be recommended.

CONCLUSIONS

In conclusion, it is clear that the chemotherapy of tuberculosis should not be undertaken lightly. All the available agents have quite definite toxic effects, and tubercle bacilli are liable to become resistant to streptomycin, dihydrostreptomycin, and P.A.S. Neither dihydrostreptomycin, the sulphones nor benzaldehyde thiosemicarbazone can at present be recommended for general use. Unless there are definite contraindications, streptomycin and P.A.S. should always be given together, but should be reserved for the types of tuberculosis which have been enumerated. Chemotherapy should never be used as a temporizing measure. It should be used only as part of a programme designed to produce arrest or cure of the disease.

TUBERCULOSIS OF THE SKIN

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THE revolution during the last five years in the treatment of lupus vulgaris is a miracle to anyone who has worked for long in a lupus clinic. The treatment of what was a distressing, disfiguring, indeed sometimes mutilating, condition was wearisome in its demands on the patient and on the doctor, and by no means sure in its effect. The chronicity and obstinacy of the disease taxed the ingenuity of the doctor and the endurance of the patient, who was submitted to tedious variations of light therapy, fierce chemicals and crude surgery. Many a patient gave up the struggle completely or from time to time. Delight at the effects of vitamin D tempered by patient assessment of its value has been followed by a bewildering number of new possible remedies; thorough trial of these, and of combinations of these, is limited in this country at least, by the apparent diminishing number of new cases.

CLASSIFICATION

While interest is so much centred on the therapeutic advances, little new has been learned about tuberculosis of the skin from the clinical and laboratory sides. The clinical types of tuberculosis of the skin depend not only upon the route by which the tubercle bacillus or its products reach the skin, but on the virulence and strain of the organism, the size of the dose, and the immunological status of the victim. The affection reaches the skin either by blood spread from a deeper seated lesion or by direct inoculation. Hence the clinical types of skin tuberculosis are usually subdivided on this basis as follows; I give the classification of Stokes (1942), based on that of Lewandowsky, Gans and Montgomery.

(A) *Localized types which spread by continuity or contiguity of tissues and by way of lymphatics*
- (1) Inoculation tuberculosis
- (2) Tuberculosis verrucosa cutis
- (3) Lupus vulgaris
- (4) Tuberculosis orificialis cutis
- (5) Tuberculosis cutis colliquativa (scrofuloderma)

(B) *Disseminated types—spread by the hæmatogenous route*
- (1) Acute generalized miliary tuberculosis of the skin
- (2) Lichen scrofulosorum
- (3) Tuberculosis cutis papulonecrotica
- (4) Lupus miliaris faciei
- (5) Erythema induratum
- (6) The sarcoid group, possibly

(C) *Other cutaneous manifestations associated with systemic tuberculosis*
- (1) Purpura

(2) Erythema multiforme
(3) Erythema nodosum
(4) Lupus erythematosus

It is evident that these will not always be clear-cut entities and that there must be overlapping cases and cases in which more than one of these types may be found, as for example, erythema nodosum and primary tuberculosis of the skin.

PRIMARY TUBERCULOSIS

This is comparable to the familiar Ghon's focus of the lung. Although it has been reported in adults, it is a disease of infants or small children, and a rarity, but probably not as rare as is usually thought. The local lesion may be so slight as to be missed or dismissed; on the other hand there may be well-marked ulceration and ultimate scar formation. Spread of the infection to lymphatics and to the glands is the rule, and the adenitis may be the first pointer to a possible tuberculous cause of a skin lesion. Enlargement of superficial glands in children always suggests the possibility of tuberculosis; that the tuberculosis in the gland may have arisen from a primary skin lesion is not so well known. The gland may break down and discharge tubercle bacilli. The course is usually towards complete regression of the skin lesion and of the glandular enlargement. Acute miliary spread of the disease is known to have happened. Erythema nodosum and other blood-spread manifestations such as lichen scrofulosorum may be related to a skin primary focus. The tuberculin skin tests are, at least in the early stages, negative. The source of the infection is usually not discovered; scratch marks or other minor trauma lay the child open to skin infection by a tuberculous adult. There are well authenticated cases which arose following ritual circumcision by operators with pulmonary tuberculosis.

TUBERCULOSIS VERRUCOSA CUTIS

The diagnosis of tuberculosis verrucosa cutis is not difficult but it is often not made; perhaps because it is not considered. As in the other types of tuberculosis of the skin, a latent awareness of its existence will precipitate the diagnosis. It can imitate the common wart, lesions due to iodides or bromides, hypertrophic lichen planus, late syphilis and, for the sake of completeness, blastomycosis. It is found classically in anatomists, pathologists, veterinary surgeons and butchers, all of whom as regards infection have I suppose much in common. Apart from contamination by handling infected material the lesions may arise from direct inoculation with the patient's own infected sputum. The lesion is made up of warty papules which run together to form patterned plaques of a brownish colour and with a typical red-blue areola. There may sometimes be exudation, even suppurative and vegetative lesions. Slow peripheral extension with partial central healing results in bizarre shapes. A special type, the 'anatomical wart' usually occurs singly on the back of a finger or thumb; the surface is markedly verrucose,

the colour is again brownish and the areola a red-blue; increase in size is negligible or very slow up to one or two centimetres in diameter. The course is essentially benign, with rare exceptions which are followed by lymphangitis and adenitis with ulceration. Success of treatment with calciferol is variable; a month of such treatment will show whether or not it is ultimately going to suffice. A combination of calciferol with streptomycin may prove to be the treatment of choice. Excision when possible of small lesions may save everyone a deal of time and trouble.

LUPUS VULGARIS

This is, of course, the most common and hence the most important manifestation of tuberculosis of the skin. The infection may reach the skin from without or from within by the blood stream, in which event the lesions may be multiple; indeed, there is an acute disseminated type of lupus which follows acute fevers, but this is a rarity. In three-quarters of the cases it is the face, particularly the nose or the lobe of the ear, which is affected; the patients are more often females in whom the disease has begun in early life. At the beginning there appear one or several grouped, pin-head sized macules of a dull red colour which slowly develop into small nodules; these have a translucent look about them, and if the affected area is blanched by stretching the skin or by pressure with a glass spatula (diascopy) they stand out as yellow-brown spots—the so-called apple jelly nodules of Hutchinson, the hallmark of lupus vulgaris. These nodules are necrotic and a pin sinks easily and softly into them as compared with the firm unaffected skin. Slow extension, measured in years, leads to the many clinical types of the disease. Nodules coalesce to form patches of disease; new nodules develop by lymphatic spread; partial healing takes place; ulceration, scarring and contraction may follow. Some patches may have creeping, gyrate edges, others may be hypertrophic, hyperkeratotic and exuberant; in some the scarring predominates, in others there is little or no scarring. Lupus makes its march in very slow time across an area, and rearguards of active nodules are always left in the midst of the scarring. Syphilis, on the other hand, quickly crosses an area, leaving inactive unadulterated scars.

Secondary infection, with lymphangitis, œdema and elephantiasis may supervene. Spread of the infection to underlying tissues, formation of deep nodules, involvement of bone, crippling of joints by adhesions or by contraction of scars, and ectropion, may all complicate the disease and the clinical picture, making the life of the patient a burden and a misery. Thus arise the many types of the disease perhaps even in the one patient, types suitably christened in Latin or in mixtures of Latin and Greek, but all fundamentally lupus vulgaris. Fortunately, new cases of mutilating or crippling lupus are now not often seen.

Lupus also attacks mucous membranes; indeed lupus of the skin of the face often arises from a focus in the nose. The mucous membrane of the nose is the most commonly affected, but the lips, the palate, the con-

junctivæ, the larynx, the pharynx, the tongue, the rectum and the vulva may all suffer. All the soft tissues of the nose may be involved; the bones themselves usually escape, but cartilage is grievously eroded, with the characteristic beak nose as the result. Diagnosis of lupus affecting the mucous membrane with no skin involvement is not always simple; it may easily be suspected, but it is another thing to be sure. Biopsy, as the good histopathologist knows only too well, is in these as in many other cases not an infallible guide to truth; what is clinically difficult is histologically difficult. On the palate the early lesions resemble a plaque of frog spawn—rather vascular frog spawn perhaps, and tending to bleed easily; ulceration may follow but perforation of the palate is unusual. In doubtful cases neglect of the Wassermann reaction may lead to a certain loss of face.

It is not surprising that the chronic irritation of lupus may cause cancer to appear. The incidence of lupus carcinoma is perhaps 1 per cent.; with present methods of treatment it should become negligible. It has long been accepted that radiation of lupus is too often followed in due time by the appearance of a malignant epithelioma. Timely wide excision of such a lesion, followed by plastic repair later when the lupus is controlled, is the treatment of choice.

Treatment.—The treatment until recently of lupus makes horrific reading; much ingenuity was applied to provide methods of destroying lupus tissue—scarification, application of caustics, blowing steam through tubes on to the lesions, Unna's thorns, freezing with carbon dioxide snow, cautery, all these had their advocates. The best results were obtained by ultra-violet light therapy, sometimes in combination with one of the foregoing. It must be said at once that the time is not yet for these methods to go on the scrap heap. That time will come only if and when the compass of the new remedies has been fully explored and found to suffice.

It would have been easier in some ways to have written on the treatment of lupus vulgaris a year or two back when views were being consolidated on the value and the methods of usage of vitamin D. Vitamin D is already overtaken in part by new preparations, and again all is flux. Results are awaited of trials of streptomycin, of *para*-aminosalicylic acid and of the sulphones. It would seem likely that combination of vitamin D with one of these may prove to be the best treatment. Calciferol is vitamin D_2, prepared by irradiation of ergosterol with ultra-violet light.

In 1848 Emery, at the Hôpital Saint Louis in Paris, achieved great success by using large doses of cod-liver oil, but one or two pints a day of this nauseating fluid was too much for the stomach of his patients and the treatment fell into disuse. It was again in France during the last war that Charpy (1943), faced with an alarming increase in the incidence of lupus vulgaris, argued that the success of ultra-violet light was due to conversion of natural sterols in the skin into vitamin D; after initial failure with small doses he was able in 1943 to report striking success. Quite independently in this country Dowling and Prosser Thomas (1945) were thinking along the

same lines, and starting in 1943, two years later they published their first results, which justified a little more cautiously the excitement of Charpy. From the end of the war, *calciferol* was tried all over the world with inevitably conflicting views on its value, its mode of action and its toxicity. The literature is full of references to these matters, but the carefully controlled and adequately followed up series of cases are few; the time is yet short. Cure, or rather arrest of the disease, is apparent clinically in a short period of time in many cases, even in three months. Histological cure is another matter, and clinical cure should never lead to early stoppage of treatment. Charpy in his first enthusiastic paper claimed cure of twenty-seven cases treated for three months, but in a later paper he reported, more judicially this time, one hundred and fifty cases treated over six years, and of these thirty had remained cured clinically and histologically for five years. It is likely from a summation of reported experience that 60 to 70 per cent. of cases of lupus vulgaris can be cured by prolonged administration of calciferol; this figure may be found to be too high as more cases are observed and for a longer period more critically. This is much the same proportion of cases as can be cured after endurance of the tedium of prolonged and persistent light therapy. However, calciferol given in large doses is not without its dangers, which seem to vary markedly in different workers' hands.

There have been many suggested variations on the original themes of Charpy and Dowling which also differed from each other. Charpy used and still champions an alcoholic solution of the vitamin; Dowling used calciferol tablets. Some dermatologists insist that calcium must be added; others give calciferol in oil; others again, say that by injection the toxic effects are reduced. Probably all the frills are unnecessary, and giving the vitamin alone is all that is required in treatment. Equally satisfactory are the original preparation of Charpy, 'sterogyl 15', 600,000 units twice a week, or calciferol tablets as used by Dowling, 50,000 units, three times a day. This dose is reduced according to the progress the patient has made after three months. Treatment will probably need to be continued up to a year or more, and in any case must be persisted in for three months after clinical cure. Although the dosage may have to be reduced because the patient's tolerance is strained, it must be remembered that a dose of 50,000 units a day is too low to be effective.

Calciferol is not a drug to be given blithely and haphazardly; all reports stress in varying degree the dangers inherent in its use. Every patient under this treatment must be under regular observation. Clinical toxic symptoms include loss of appetite, thirst, polyuria and frequency, headache, giddiness, weariness, loss of weight and abdominal pain. Routine examinations of the urine for albumin, the blood urea and serum calcium are required as a precaution and abnormal findings are indications for temporary stoppage of the drug. An increase in the blood sedimentation rate is another sign of toxicity. Because of the risk of kidney damage or of metastatic calcification the drug should be withheld in the presence of arteriosclerosis, albuminuria

or kidney disease. Rather curiously it sometimes causes an exacerbation of active pulmonary tuberculosis, another contraindication to its use. Toxic effects may arise in up to 20 per cent. of cases; so that there is still a place for the long-established methods of local treatment. Nor must it be forgotten that these patients have tuberculosis and need rest of mind and body, good food and healthy surroundings.

Evidence is slowly being collected to show that *streptomycin* and calciferol have a synergistic effect. It is good practice to start treatment with streptomycin, 1 g. daily for four to six weeks, together with calciferol continued after this period as in the previous schemes.

TUBERCULOSIS ORIFICIALIS CUTIS

This is a condition more familiar to those who work in sanatoria as it is an affliction of patients with known and advanced tuberculosis of internal organs; rarely it may be the presenting sign of deeper seated mischief. The mouth is the most common site for this lesion, a tuberculous ulcer developing on the tongue, usually on the side or on the tip. The ulcer is round or oval, well defined and not very deep; pain is present in varying degree and may be intense. Scrapings from the granulating base of the ulcer may show tubercle bacilli. Similar lesions may be found around the anus in a patient passing bacilli in swallowed sputum or with intestinal tuberculosis. The external genitalia may also be affected by this type of ulcer. Treatment is directed towards the primary lesion. Symptomatic treatment of the ulcers is clearly difficult so long as reinfection of the site is constantly recurring. Excision, rather surprisingly, may relieve the patient from the misery of a lesion on the tongue. Anæsthetic lozenges give temporary relief and allow a meal to be taken in relative comfort.

SCROFULODERMA

This term covers involvement of the skin by spread of infection from an underlying tuberculosis of glands, bones or joints; or it may arise following operation, for instance, after removal of a tuberculous kidney. The most common site for the lesion is over the cervical glands; following caseation and breakdown of the glands the skin over them becomes purple red, doughy, and later, perhaps after many months, ulcerated, with multiple sinuses communicating with the deeper structures. Scarring distorts the diseased area. The superficial infection may spread over the surrounding skin in the form of lupus. At any stage of its development the condition may be arrested. Under this head may be included the tuberculous gumma, a subcutaneous nodule which enlarges to walnut size and implicates the skin over it. Treatment of scrofuloderma is primarily that of the underlying disease. Local application or injection of streptomycin is a present possibility.

BLOOD-SPREAD INFECTIONS

Tuberculosis miliaris disseminatus.—This is acute miliary tuberculosis

FIG. 1.—Acne agminata.

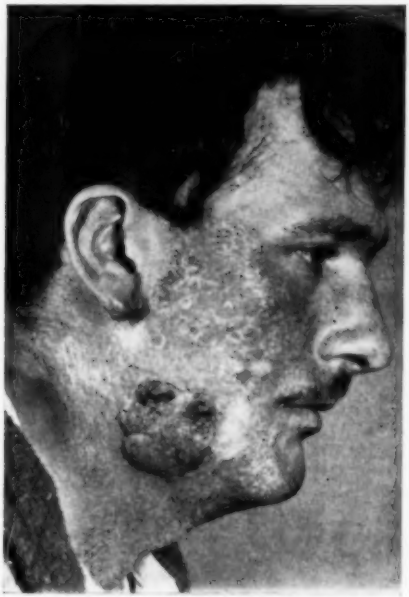

FIG. 2.—Lupus carcinoma.

FIG. 3.—Anatomical wart.

FIG. 4.— Lupus verrucosus cutis.

involving the skin and is associated with evidence of tuberculosis elsewhere in the body. The lesions, although they contain tubercle bacilli, are not specific and range from purpura to vesiculation.

Lupus miliaris disseminatus faciei.—This is not common; quite suddenly and symmetrically crops of well-defined patches of closely packed discrete, tiny lupoid macules which enlarge into papules appear on the face. It might be confused with acne rosacea, but it lacks the florid, expensive looking character of that condition, usually spares the nose, and is altogether a more uniform and less assertive eruption. The course is benign with slow progression to cure in up to two years, leaving small pitted scars. Calciferol therapy is disappointing. Two cases treated by me with streptomycin after failure with calciferol improved remarkably, only to relapse. Tuberculosis elsewhere is theoretically always present; it is often not found.

Lichen scrofulosorum.—Fifty years ago this was not uncommon—5 per cent. of skin cases in children, Radcliffe-Crocker (1903) estimated; now it is not often seen. Rings or patches appear quite suddenly in scrofulous children, patches made up of pin-head sized lichenoid follicular papules, red at first but fading even to the colour of normal skin. There may be a little superadded scale and rarely necrosis. The eruption is usually limited to the trunk, and after varying periods regression is complete. The disease is an indication of an active tuberculous process somewhere in the body. It is interesting that the response to a 'jelly' tuberculin patch test may be a localized lichen scrofulosorum.

Tuberculosis papulonecrotica.—This is a large group variously named and variously subdivided by different authors. The essential lesion is a chronic, brownish-blue, shot-like papule, discrete but sometimes grouped, which may break down into a transient pustule healing with a tiny sunken brown scar. Special types are found on the face, known variously as acne agminata, disseminated follicular lupus, and acnitis. The condition may arise at any age but is commoner in adults. Crops break out from time to time and the whole thing may last from six weeks to many years. Treatment is, to put it vaguely, constitutional; calciferol is not dramatic in these cases but is usually given.

Erythema induratum (*Bazin's disease*).—This disease is one of those conditions which like 1066 everyone remembers by name; remembering does not always lead to proper recognition. It occurs much more often in females than in males; in females in the second decade with those plump, blue legs which permanently look cold and usually are. The lesions develop slowly and symmetrically as deep, painless nodules on the backs of the legs, although the arms do not always escape; these slightly tender nodules enlarge and some run together to form plaques; after weeks or months the skin over them becomes even more livid than its normal. Regression may begin at this stage, or necrosis and indolent ulceration may follow, finally leaving a thin, slightly puckered brown scar. One attack confers no immunity; so that recurrences of what is in each attack a persistent disease are

FIG. 5.—Lupus vulgaris.

FIG. 6.—Lupus vulgaris.

FIG. 7.—Lupus vulgaris.

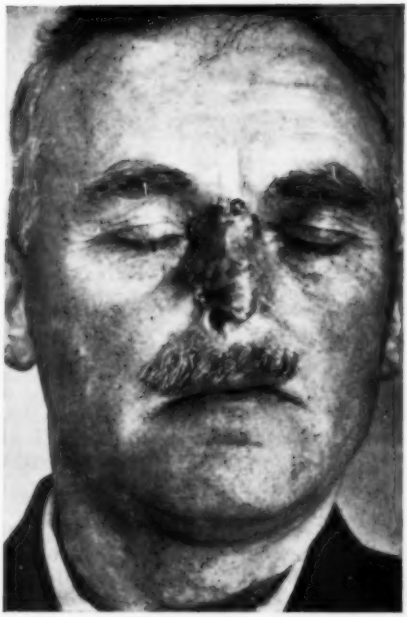

FIG. 8.—Lupus vulgaris.

FIG. 9.—Erythema induratum.

well recognized. The diagnosis does sometimes present difficulties even from ordinary chilblains, but these are much more superficial. Syphilitic gummas are usually single, and when multiple are not symmetrical and occur in an older age-group. Erythema nodosum is a much more acute, sometimes febrile condition, found more on the fronts than on the backs of the legs, with lesions which are ill defined, brighter red in colour, painful and tender. Whitfield described another erythema induratum in older women with bad teeth and deep plaque-like lesions in the thighs as well as in the legs. This last condition is probably a streptococcid and is easier to cure than Bazin's disease; in fashionable quarters it is now called nodular vasculitis. Treatment of Bazin's disease may depend upon that of some other focus in the body but the other focus is only too often elusive. It is difficult to persuade patients even with quite unattractive ankles to wear thick stockings and well-lined boots, but that is what these patients should do in cold weather. Firm crêpe bandaging maintains heat and perhaps supports the sluggish circulation. Heat in the various forms offered by the physiotherapists is at least comforting and may do good. Calciferol is usually disappointing; what the new remedies will do is still unlearnt.

OTHER MANIFESTATIONS

The non-specific eruptions which may be associated with tuberculosis elsewhere are erythema nodosum, erythema multiforme, and purpura. These belong to the group of toxic eruptions and may arise from several causes, among which tuberculosis must be borne in mind. Lupus erythematosus, particularly the more infiltrated doughy type, may have a tuberculous basis. It is interesting that following treatment with ultra-violet light or with calciferol, lupus vulgaris may be converted into clinical lupus erythematosus. The sarcoid group is too large for discussion here, but there is a growing consensus of opinion that the greater proportion of these cases is tuberculous in origin.

CONCLUSION

What of the not very distant future? The surge forward is going to continue, but in which of many possible directions it cannot be said. Calciferol, *para*-aminosalicylic acid, antibiotics, sulphones, singly and in combination, by mouth, by injection and by local application, all await eager trial.

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TUBERCULOSIS OF THE GENITO-URINARY TRACT

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Lesions of tuberculosis which appear in the different parts of the genito-urinary tract are visceral manifestations of a general disease. Tuberculosis is a generalized infection with focal manifestations. This infection is characteristically contracted during infancy or youth. The tubercle bacillus may be implanted as an air-borne infection by inhalation, or it may be ingested. Thus the tubercle bacillus may be harboured in the atmosphere and dust of the home or factory, or it may be ingested from contaminated food, and in particular from infected milk.

PHASES OF DEVELOPMENT

The various phases of the manifestations of tuberculosis in the human body have a similarity to those of syphilis. The cycle of events may be described under four headings which, in their relation to the stage of the disease, date from the time of the penetration of the tubercle bacillus to the human body to the most advanced lesions of visceral caseo-cavernous tuberculosis.

(1) *Period of incubation.*—This stage in the cycle of tuberculous infection is a latent period following the implantation of the tubercle bacillus to the body, and this period persists until a positive cutaneous reaction appears, which is the first manifestation of an allergy to the tubercle toxin.

(2) *Period of invasion.*—The second period is that of the first invasion of the tubercle bacillus when the infection reaches the lymphadenoid system. It is a stage which is generally silent so far as clinical manifestations are concerned, although sometimes associated with intermittent fever, indeterminate lassitude, and anæmia. Lymphadenoid enlargement may be appreciated, and as this stage of invasion continues and lymphadenoid resistance is maintained, calcification in lymph nodes may become apparent on radiological examination. The cutaneous reaction persists.

(3) *Period of visceral spread.*—The third period is that stage in the disease when lymphadenoid resistance has been overcome, and the lymphatic system by its centripetal flow empties into the blood stream all organisms which reach the great lymphatic trunks. Implantations of tubercle bacilli are blood-borne to the lungs. It is the stage of visceral spread. Lesions appear in the lungs as localized areas of a caseo-pneumonic or broncho-pneumonic process, usually at the apex of the lung. There is often an accompanying sero-fibrinous pleurisy. Meanwhile, however, implantations of tubercle bacilli may reach the bones, joints or other organs *via* the blood

FIG. 1a.—Retrograde pyelogram (left): irregularity of the upper minor calyx, suggesting early cavity formation. Bacteriological examination: tubercle bacilli, human type, obtained from specimens of urine from the bladder and left ureter.

FIG. 1b.—X-ray of kidney showing small calcified deposit in upper calyx.

FIG. 1c.—Drawing of kidney.

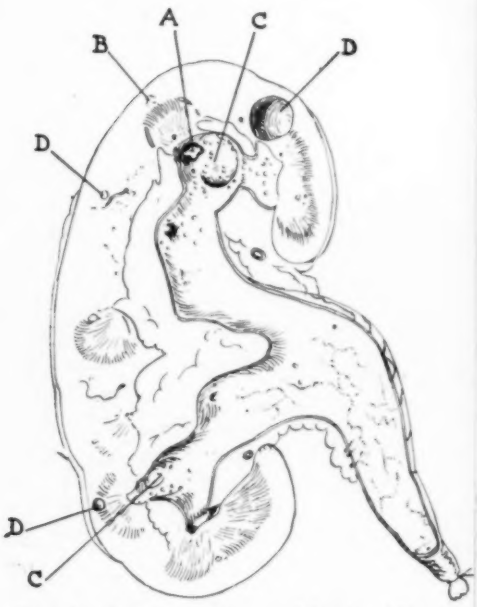

FIG. 1d.—Explanatory diagram of drawing: (A) calcification in tuberculous focus; (B) small focus in cortex; (C) papillary involvement; (D) small congenital cyst.

FIG. 1e.—Photograph of whole section.

FIG. 1f.—Microscopic report. Eight or nine small fibro-caseous tuberculous follicles are present round the margin of the upper calyx. Similar, but healed, lesions are present in the cortex above. The cyst is smooth-walled and of congenital origin.

Figure 1a to f are reproduced by permission from Winsbury-White's 'Textbook of Genito-Urinary Surgery', published by Messrs. E. & S. Livingstone Ltd.

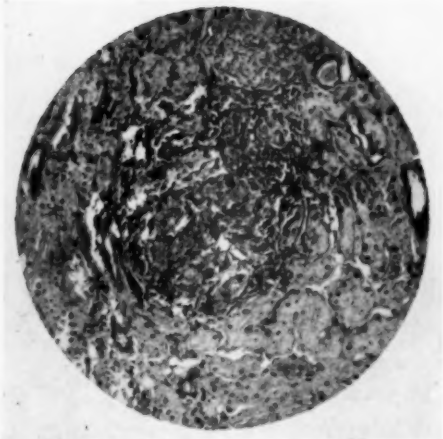

FIG. 2.—Bacilluria. Minute cortical focus showing early epithelioid tubercle follicle and glomerulus.

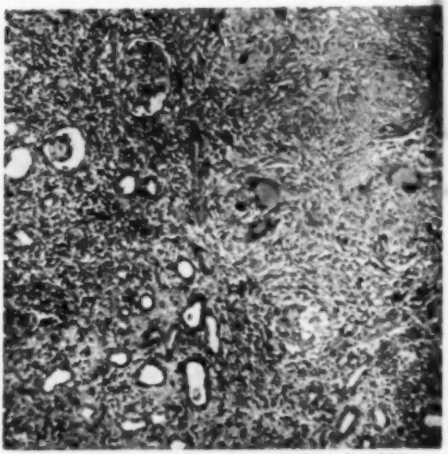

FIG. 3.—Healing tuberculous lesion in kidney: fibrosis, giant cell formation, minimal caseation.

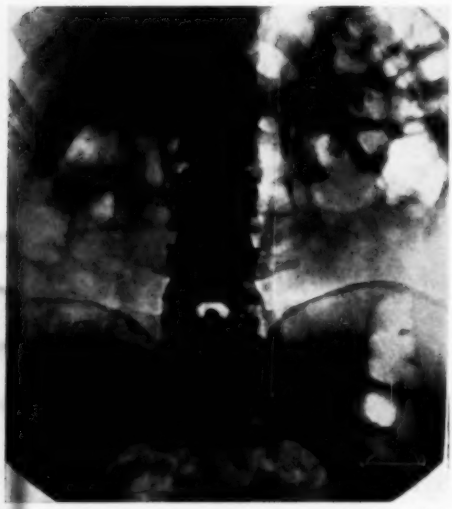

FIG. 4.—Intravenous pyelogram following left uretero-colic anastomosis. Male, aged twenty-two years. Contracted tuberculous bladder following right nephro-ureterectomy for tuberculosis. The renal function has been well maintained, and urination per rectum has been at normal intervals with full control.

FIG. 5.—Male, aged thirty-six. Cutaneous ureterostomy with skin pedicle nipple for tuberculosis of the remaining right kidney. The contracted tuberculous bladder led to incontinence owing to excessive frequency of micturition.

FIG. 6.—A Pierce Wet colostomy bag (Salt & Son, Ltd., Birmingham) has been adapted for cutaneous ureterostomy with skin pedicle nipple.

FIG. 7.—Method of applying ureterostomy bag. The hole in the rubber flange is cut to fit the skin pedicle.

stream. The nature of the lesions produced in the tissues by the tubercle bacillus depends upon (a) the number and virulence of the organisms, and (b) the resistance of the host.

The lesions may be sparse or miliary, active or relatively quiescent. Should the original infection during the first period of incubation be massive, the second period of invasion follows a rapid course and metastatic foci of infection may become fulminant and rapidly fatal. Should the second period of invasion be resisted by the lymphadenoid system, and the leakage of tubercle bacilli to the blood stream remain sparse and infrequent, the lymphadenoid system tends by sclerosis to overcome the original implantations in the lymph nodes, and metastatic foci of infection are subsequently rare in their appearance and slow in their development.

(4) *Period of advanced caseo-cavernous pulmonary tuberculosis.*—The fourth period in the cycle of tuberculous infection is that of phthisis, characterized by extensive ulcero-cavernous or caseo-cavernous lesions in the lung. Caseo-cavernous pulmonary tuberculosis is the last phase of tuberculosis. It is rare to find renal tuberculosis in sanatorium patients suffering from pulmonary tuberculosis; thus, in a personal series of 64 cases of tubercle bacilluria in patients suffering from extra-urogenital tuberculosis, only three developed clinically recognizable renal tuberculosis with positive pyelographic findings, i.e., a percentage comparable to the 6 per cent. incidence of renal tuberculosis in phthisical patients quoted by French authors (Cibert, 1946).

In the evolution of renal tuberculosis it would appear that the implantations of tubercle bacilli reach the kidney at a stage in the disease long before the fourth period when there are gross caseo-cavernous lesions in the lung. It is probable that it is in the third stage of tuberculosis as a general infection, when tubercle bacilli are escaping from the lymphadenoid system to the blood stream, that the earliest minute foci appear in the kidney. It is in this stage when lymphadenoid resistance has been overcome, and an intermittent but sparse hæmatogenous dissemination of tubercle bacilli is taking place, that those minute implantations occur in the renal cortex which give rise to tubercle bacilluria. As a rule, patients who in this manner receive their earliest implantations of tubercle bacilli to the kidney have very nearly, but not quite, overcome the tuberculous infection in its second stage of invasion.

In the management of patients suffering from genito-urinary tuberculosis, it is always necessary for the physician and surgeon to bear in mind that the evolution of renal tuberculosis must be antedated to a period in the patient's life history when resistance by the body to invasion from tubercle infection was incomplete. This stage may have been in childhood or adolescence. Renal tuberculosis is the result of a hæmatogenous dissemination of the tubercle bacillus to the viscera, and consequently such patients must be regarded as individuals who require complete and systematic clinical and radiological examinations. They are individuals who must be regarded as potentially liable to harbour extra-urogenital foci of tuberculous infection.

Such foci may remain quiescent during surgical intervention, or they may become reactivated, depending upon the virulence of the tubercle bacillus and the powers of resistance of the patient. The blood sedimentation rate, the blood count, the examination of sputum and urine for tubercle bacilli, the estimation of the sensitivity of the tubercle bacillus to streptomycin, all require to be taken into consideration before an assessment may be made as to the timing of the surgical intervention or the type of operation which may be considered necessary in the treatment of genito-urinary tuberculosis. If such an assessment is to be made conscientiously, patients suffering from genito-urinary tuberculosis should be observed under sanatorium conditions for an indeterminate period before, during and after surgical intervention. It is obviously essential for physician and surgeon to work in close collaboration, so that the treatment of tuberculosis as a generalized infection may never be lost sight of, and surgical interventions regarded merely as incidents in the therapy of the disease.

THE SIGNIFICANCE OF TUBERCLE BACILLURIA

It was at one time considered that tubercle bacilluria indicated the passage of tubercle bacilli (in a tuberculous patient) through a perfectly healthy kidney, or a kidney damaged in any way but not tuberculous. This view has now been disproved by many observers. In a personal series of three hundred cases of extra-urogenital tuberculosis, tubercle bacilluria was found present in 21.3 per cent. In this series, autopsy examination of thirty patients, who had died without having developed symptoms or signs of genito-urinary tuberculosis, revealed in serial sections of the kidney minute cortical tuberculous foci in every case. All stages of development of the tubercle follicle, including epithelioid, giant cell formation, and caseation, were noted. In many the scars of healed follicles were present. These minute tubercle follicles, constantly present where there had been tubercle bacilluria, were never visible to the naked eye. The follicles developed in relation to the glomerulus and were found in the cortex and in the cortico-medullary zone of the kidney (fig. 2). Although many patients in a sanatorium population developed bacilluria in the terminal phases, tubercle bacilluria was a temporary feature and finally disappeared in 23.4 per cent. This recovery rate was associated with healing of the extra-urogenital lesions which had led to the admission of the patient to the sanatorium. It is considered that the minute cortical follicles which had led to the tubercle bacilluria had been the result of a hæmatogenous dissemination of the bacilli. This occurs, as has already been mentioned, during the period of visceral spread or the third stage in the cycle of tuberculosis. Probably because the leakage of implantations of tubercle bacilli to the blood stream had remained sparse and infrequent and the patient's general resistance had been built up under sanatorium conditions, many of these little follicles healed or became encysted by sclerosis, and thus the tubercle bacilluria ceased. In the management of tuberculosis, tubercle bacilluria must be regarded as evidence that

the second invasive stage of tuberculosis has been successful, and the third stage of visceral spread has started. Nevertheless, adequate measures taken to build up the patient's resistance, and antibiotic or other therapy directed towards such tuberculous lesions as are demonstrable, may lead to permanent cessation of tubercle bacilluria and the return of the patient to health and strength (fig. 3). Frank renal tuberculosis following tubercle bacilluria occurs in a very low percentage of patients. Therapeutic measures for the treatment of bacilluria should be as intensive and prolonged as for the treatment of any other clinically recognizable focus of tuberculous infection.

THE PATHOGENESIS OF RENAL TUBERCULOSIS

The characteristic lesion in an early ulcero-cavernous renal tuberculosis is a lesion which has led to cavity formation in the kidney, demonstrable by pyelography. From the minute cortical foci which follow hæmatogenous dissemination of tubercle bacilli to the organ, tuberculous debris passes *via* the tubules where they converge at the apex of the pyramid. The pyramid and papilla are exposed to infection (a) from tubular extension, and (b) by direct spread from foci in the cortico-medullary zone. Thus, a confluence of follicles at the papilla leads to ulceration and cavity formation which communicates with the renal pelvis. Pyelographic examination, whether by intravenous or retrograde method, can only demonstrate the tuberculous kidney when the irregular outline of the calyx system reveals the communication of the calyx with a tuberculous cavity in the parenchyma (fig. 1a). The time factor in the pathogenesis of renal tuberculosis is that of a long-continued ulcerative process. As the course of tuberculosis fluctuates as extra-urogenital lesions heal or become encysted, or as the patient's general resistance rises and falls, the tempo of the ulcero-cavernous process in the kidney alters, but when the lesion in the kidney becomes cavernous and tuberculous debris reaches the renal pelvis in such quantities as to cause pyuria, the infection spreads throughout the renal pelvis and descends *via* the ureter to the bladder. The first symptoms of renal tuberculosis are those of infection of the bladder and frequency of micturition. The chronicity of renal tuberculosis and the attempts at healing by fibrosis and calcification may be noted clinically by the straight X-ray of the renal region, or by the presence of minute areas of calcification in the kidney dissected after removal (fig. 1, b, c and d). The relationship of the ulcerated lesions at the papilla to the corresponding foci in the cortex is shown in fig. 1, b, c and f.

TREATMENT OF RENAL TUBERCULOSIS

It is only by surgical removal of the tuberculous kidney that cessation of the continued reinfection of the bladder can be brought about. Nephro-ureterectomy is the treatment of choice. The chronicity of renal tuberculosis and the latency of visceral spread in relation to the second invasive stage of tuberculosis raise important points for the consideration of physician and surgeon. If the patient is to be reviewed clinically with regard to all aspect

of tuberculosis, there should be admission to hospital under sanatorium conditions so that extra-urogenital foci of infection may be identified or excluded. The blood sedimentation rate and bacteriological examinations of the urine should be ascertained from time to time. The sensitivity of the tubercle bacillus to streptomycin should be known. At the same time the state of the opposite kidney should be investigated. In many clinics retrograde pyelography is deprecated, but the knowledge that a pyelogram of the opposite kidney is normal and that a specimen of urine obtained from the opposite renal pelvis is sterile and free from pus cells, is a matter of supreme importance to the surgeon and patient, if nephro-ureterectomy is contemplated. Thanks to chemotherapy and the state of well-being that sanatorium treatment alone may bring to patients with renal tuberculosis, nephro-ureterectomy can be delayed until conditions for operative intervention are at their best—'la néphrectomie opportune' of de Beaufond (1947).

Chemotherapy.—At the present time, in addition to preliminary observations and treatment under sanatorium conditions, streptomycin and *para*-aminosalicylic acid (P.A.S.) may be employed in the preparation of the patient for operation, and the chemotherapy continued throughout convalescence until the total dosage required for the patient has been attained. The use of chemotherapy in preparation for operation should give the surgeon greater confidence in extending the scope of the operation to include not only removal of the kidney, but also the entire ureter to just above the bladder. Chemotherapy should minimize the risks of a second incision to complete the removal of the ureter without fear of wound contamination. The surgery of access is important, and free exposure of both kidney and ureter should avoid traction at wound margins such as would predispose to wound infection and chronic sinus formation. Chemotherapy does not replace gentleness in the handling of tissues for successful operative surgery.

RESIDUAL ULCERATION IN THE TUBERCULOUS BLADDER

Although the operative mortality of nephro-ureterectomy in tuberculosis is low, the late disability from residual ulceration of the bladder is high, and may be as much as 50 per cent. Persistent vesical ulceration with pyuria and the presence of tubercle bacilli in the urine may be reduced in incidence by deliberate nephro-ureterectomy, and the use of a second lower abdominal incision to ensure that the ureter is removed as close to the bladder as possible. The completeness of the surgical intervention, however, is not the only means of bringing about an amelioration of vesical symptoms. As has already been mentioned, the timing of the operation when the patient has achieved the highest possible state of well-being while under observation in the sanatorium and while undergoing a prescribed course of chemotherapy, is a matter of the utmost importance in the management of urinary tuberculosis. Even without chemotherapy, marked amelioration in vesical symptoms can be achieved by a sanatorium regimen alone. Nephro-ureterectomy is an operation of necessity in that it removes the source of the vesical infection,

but the building up of a patient's resistance by natural means, as well as by chemotherapy, is of equal importance if the operation is to be well borne and to yield a higher standard in the late results.

THE RESULTS OF CHEMOTHERAPY

In a clinical study of the use of streptomycin in urinary tuberculosis, patients were divided into five categories (Jacobs and Borthwick, 1950):—

Group 1: Unilateral renal tuberculosis—minor lesion without cystitis.
Group 2: Unilateral renal tuberculosis—major lesion necessitating nephrectomy: cystitis.
Group 3: Bilateral renal tuberculosis—nephrectomy for the more advanced lesions.
Group 4: Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease.
Group 5: (a) Major bilateral tuberculous lesions.
(b) Minor bilateral tuberculous lesions.

In Group 2, in which the patients suffered from a unilateral renal lesion with associated cystitis, the kidney was removed soon after the initial investigation had been completed. In this group fourteen patients had streptomycin therapy, and tubercle bacilli disappeared from the urine in twelve. In two cases of severe cystitis, marked contracture of the bladder occurred soon after the beginning of treatment, and there was a worsening of the clinical state. As a result of this clinical investigation, it was concluded that in cases in which there had been a unilateral renal lesion and nephrectomy had been carried out, cystitis was relieved, and the urine became tubercle-negative in an appreciably larger number of streptomycin-treated cases than had occurred in a similar group used as a control. The authors commented further, however, that the administration of streptomycin to those suffering from urinary tuberculosis is not an alternative to prolonged sanatorium care, or to nephrectomy when the renal lesion is a unilateral one.

It has been customary to employ P.A.S. (*para*-aminosalicylic acid) with streptomycin, but it is my impression that in certain cases the use of P.A.S. appears to aggravate the vesical symptoms. Following nephro-ureterectomy, sanatorium treatment, with or without chemotherapy, is necessary over a prolonged period if the vesical ulceration is to be given a chance to resolve. The longer the history of vesical symptoms before the patient comes under observation with a view to nephrectomy, the longer the period of post-operative sanatorium care must continue.

In recent years, Lane of Dublin has been using dilute solutions of synthetic anti-tuberculous substances for bladder lavage. The use of these substances has followed on a study of the structure of chaulmoogric acid (Barry and Twomey, 1947). The antibacterial action of dialkyl succinic acid, in a dilution of 1 in 400,000, inhibited the growth of the tubercle bacillus *in vitro*. Lane (1950), in a personal communication, considered that the instillation of small quantities of dilute solutions of such an acid to the bladder, by its attack on the envelope of the tubercle bacillus, may render the bacillus more susceptible to streptomycin, and hasten the resolution of residual vesical tuberculosis.

POST-NEPHRECTOMY VESICAL CONTRACTURE

(1) *With the remaining kidney healthy.*—In a small group of cases persistent vesical ulceration leads to a bladder so contracted that the capacity does not exceed 100 ml. under anæsthesia. The constant frequency of micturition, amounting in effect to incontinence, gives rise to a crippling disability for which a portable urinal may be employed. Further, the contracture of the bladder wall and the constant systole of repeated acts of micturition lead to an increasing backward pressure to the remaining kidney and ureter. Late after nephrectomy, hydronephrosis and hydroureter of the remaining kidney more commonly lead to uræmia and death than bilateral renal tuberculosis. Intravenous urograms taken at follow-up examinations provide essential guides to the future management. Should chemotherapy and sanatorium conditions prove useless, however, and should freedom from extra-urogenital lesions be established, deviation of the urine from the bladder is a procedure which can prolong life in comparative comfort for many years. For those who are of a younger age-group, and are otherwise fit, uretero-colic anastomosis is an operation of undoubted value. The anastomosis may be done by the extraperitoneal and transperitoneal routes. Accurate suture of the mucosa of the ureter to the mucosa of the bowel will prevent leakage and avoid the need to bury unduly the transplanted ureter in a sero-muscular channel in the wall of the colon (Cordonnier, 1949). After such a defunctioning procedure, the bladder invariably heals. The restoration to the patient of a regular habit of urination per rectum is reflected by a gain in weight and well-being, associated with more regular hours of sleep. Modern operative technique and chemotherapy have rendered uretero-colic anastomosis preferable to cutaneous ureterostomy when the remaining kidney is healthy (fig. 4).

(2) *With the remaining kidney diseased.*—When there are changes in the remaining kidney with impairment of function, uretero-colic anastomosis may offer little prospect of success. The kidney may already show hydronephrotic dilatation, or there may be irregularities of the walls of the calyces indicative of tuberculous ulceration. Persistence of numbers of tubercle bacilli in the urine with pyuria is suggestive of tuberculosis of the remaining kidney, except in the male, in whom genital foci of infection as a source of reinfection of the bladder must be excluded. Tuberculous ulceration and stenosis of the lower end of the remaining ureter may be found less rarely. Should the vesical infection respond to chemotherapy, renal function may still be restored by deviation of the urine.

Cutaneous ureterostomy is the simplest of methods for the deviation of urine from the bladder. Difficulties in devising suitable types of collecting apparatus without the use of ureteric catheters had led to the operation losing favour with many surgeons. For the past few years my colleague, Mr. A. B. Wallace, has collaborated in the preparation of cutaneous pedicle tubes into which the exteriorized ureter may be drawn. The operation is illustrated diagrammatically in fig. 8. We first used this method of cutaneous ureterostomy with skin pedicle nipple in order to overcome incontinence, and so rehabilitate female patients suffering from vesical paralysis due to permanent

lesions of the spinal cord. The adoption of the Pierce Wet colostomy bag has proved satisfactory as a collecting apparatus when the skin pedicle tube is of adequate size to penetrate the opening to the bag (fig. 5, 6, 7). This method has recently been adopted when tuberculosis of the remaining kidney and backward pressure from a contracted bladder have led to deterioration in renal function. In such circumstances, the free drainage provided by the ureterostomy slows down the progress of the renal lesions, and renal function is improved. An easily applied collecting apparatus restores to the patient a sense of well-being which renders much more remote the prospect of an ultimate decline (fig. 5).

GENITAL TUBERCULOSIS IN THE MALE

There is a coincidence of renal and genital lesions in tuberculosis in more than 50 per cent. of cases. It is likely that persistent vesical infection in the male after nephrectomy is more commonly due to reinfection of the bladder

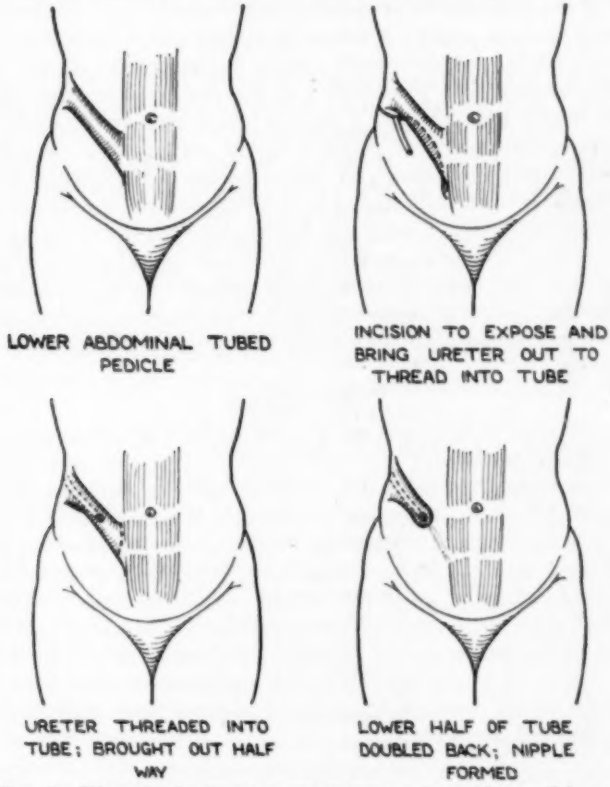
LOWER ABDOMINAL TUBED PEDICLE
INCISION TO EXPOSE AND BRING URETER OUT TO THREAD INTO TUBE
URETER THREADED INTO TUBE; BROUGHT OUT HALF WAY
LOWER HALF OF TUBE DOUBLED BACK; NIPPLE FORMED

FIG. 8.—Diagram of cutaneous ureterostomy using a skin pedicle to form protuberant nipple.

from the genital organs than was formerly believed. Borthwick (1946) reported the high incidence of foci in the prostate and seminal vesicles in genital tuberculosis. Tuberculous epididymitis is, unfortunately, a peri-

pheral extension of the disease *via* the ductus deferens. The nodule of tuberculous epididymitis is readily noted by patient and surgeon soon after its appearance. Tuberculous prostatitis and seminal vesiculitis cannot be recognized before the rectal examination is made. All cases of tuberculous epididymitis should be treated as cases of urogenital tuberculosis and subjected to the same investigation as in-patients under a sanatorium regimen. In over 80 per cent. of such cases there is bilateral seminal vesiculitis (Borthwick, 1946), and in over 50 per cent. there are coincident renal lesions. The general management of such patients is as has been described for cases of renal tuberculosis. The clinical investigation should be complete, and bed rest and chemotherapy prescribed. In all cases the affected vas deferens should be ligated and divided, and at the same time an epididymectomy performed. If the contralateral epididymis and seminal vesicle are healthy, no more need be done while the patient is in hospital under chemotherapy. With a favourable response to such a minor operation, and full conservative treatment, fertility, with preservation of the remaining vas deferens, may continue. Should the contralateral seminal vesicle show evidence of thickening, however, the disease will certainly spread *via* the vas to the remaining epididymis, with the possibility of further spread to the testis. Ligation of the contralateral vas is indicated in such circumstances, in order to protect the remaining epididymis. Infertility has already occurred as a result of the diseased vesicle. Castration in young men is an operation that should be deplored. The time factor necessary for appropriate conservative treatment, chemotherapy, and opportunely planned epididymectomy and ligation of the vasa deferentia, is negligible if the testes with their hormonal secretions can be preserved.

CONCLUSION

In the management of genito-urinary tuberculosis the advent of streptomycin therapy renders collaboration between physician and surgeon a matter of supreme importance if surgical interventions are to be carried out at the most opportune time in the course of the disease. The later disabling factors in genito-urinary tuberculosis, such as persistent vesical ulceration and contracted bladder, have a frequent incidence after successful nephroureterectomy. Streptomycin therapy combined with sanatorium supervision, before and after the operative intervention, may lead to a considerable reduction in the incidence of persistent vesical ulceration, with a tubercle-positive urine. It is recommended that patients suffering from genital tuberculosis should have the opportunity of sanatorium facilities for their investigation and treatment.

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THE PRESENT STATUS OF SURGERY IN PULMONARY TUBERCULOSIS

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THE surgical treatment of pulmonary tuberculosis, in essence, resolves itself into the treatment of the tuberculous cavity, and for the sake of clarity it is necessary briefly to outline the process of formation, the causes of persistence, and the mechanism of closure of such cavities.

CAVITY FORMATION AND PERSISTENCE

After the tubercle bacillus has gained entry into the lung of a susceptible individual, the tissues react classically with the formation of tuberculous granulation tissue. The fate of the focus depends upon the resistance of the patient against his disease and the size of the focus. If both factors are favourable, restitution to almost normal may occur. Usually, however, caseation occurs, owing to the diminution of the blood supply resulting from the endarteritis of the vessels supplying the focus. At this point, if the level of the patient's resistance is raised and the focus is small, the focus may become encapsuled, with or without calcification. In the progressive case, however, neighbouring foci coalesce to form an abscess. This abscess, as with progressive tuberculous foci elsewhere, sooner or later ruptures on to the surface of the body, in this case into the bronchial tree, air entering the cavity thus formed by the discharge of tuberculous pus.

The reason for the persistence of the cavity is to be found in the condition of the draining bronchi. Any cavity in the lung, for example an acute lung abscess, will close spontaneously if there is free bronchial drainage, by virtue of the elastic tissue in the lung, which is attached to the bronchi, but encloses circumferentially the area of lung tissue supplied by the bronchi concerned. If the drainage of such an abscess be interfered with, usually by a lung slough, the abscess cavity persists. The mechanism in tuberculosis is different. During the ulceration of the abscess into the bronchial tree the affected bronchi are involved in the pathological process. The juxta-cavitary portions of the bronchi are completely replaced by tuberculous tissue; more centrally, only the mucosa is so replaced, and more centrally still the tuberculosis affects only the submucosa, at first continuously, and afterwards in isolated areas; the submucosa, however, for a considerable distance shows an increased vascularity. The sum total of these changes is a diminution in the calibre of the bronchial lumina, and this, in essence, is the reason for the persistence of the cavity. During inspiration, normal bronchi are both lengthened and widened; during expiration the reverse takes place: the

bronchi shorten and become narrower. A bronchus affected by tuberculosis behaves in the same way, but because the lumen is already considerably diminished there is a period during expiration when the lumen is closed. In a case with cavitated disease, during inspiration the negative pull on both the cavity walls and the bronchi opens both, and air enters the cavity. During expiration air leaves the cavity and continues to do so until the point at which the bronchus closes as a result of the partial stenosis; in other words, air is trapped in the cavity as a result of a partial expiratory stenosis.

There is a further ill-effect of this mechanism, in that the mean pressure of the air thus trapped in the cavity is greater than atmospheric pressure, and this mean positive pressure on the walls of the cavity embarrasses its blood supply and in consequence the local defence mechanism. Thus the partial stenosis of the draining bronchi is not only the cause of persistence of the cavity, but also of the disease itself.

The preceding remarks apply to cavity formation in the relatively early stages of the disease. In the later stages, when there is considerable pulmonary fibrosis, and the lung itself is firmly fixed to the chest wall, the bronchial element may not be the chief factor in causing persistence of the cavity, as by this time the cavity is, as it were, attached directly to the chest wall, and this maintains the patency of the cavity.

CAVITY CLOSURE

From the foregoing it will be appreciated that, apart from considerations of the patient's innate resistance against the infection, the problem is the mechanical one of a partial expiratory stenosis, giving rise to a mean positive pressure within the cavity, and if these factors can be overcome, the patient has a reasonable prospect of being cured of his disease. This can be brought about by: (1) eliminating the bronchostenosis; (2) preventing air entering the cavity during the inspiratory phase; or (3) by decompressing the cavity in such a way as to prevent a positive pressure building up in the cavity.

(1) The best example of *elimination of the stenosis* is that resulting from the use of *streptomycin*. The beneficial effects of this antibiotic on tuberculous bronchitis have been shown in cases in which the larger bronchi are affected, and the progress of treatment can be controlled visually by means of bronchoscopic examination. Theoretically, to say the least, it is possible that such improvement in the tuberculous endobronchitis may take place as a result of bed rest and, as a result of establishing free drainage, the cavities close; another possible, and perhaps more probable, explanation of the satisfactory results achieved by bed rest is that, resultant upon the decreased oxygen requirement during bed rest, the patient's respiratory movements are so decreased as to maintain closure of the bronchus during the whole respiratory phase; the mechanism which falls under the second heading.

(2) The *prevention of air entering the cavity*, as indicated above, is pro-

cured by maintaining the walls of the draining bronchi in apposition during the whole respiratory phase. This may be brought about during bed rest, which might be termed passive relaxation, or by active relaxation, by either pneumothorax treatment, thoracoplasty or one of the other forms of relaxation therapy. During pneumothorax or mechanically similar form of treatment, the lumen of normal bronchi is further decreased, and thus the partially stenotic bronchus is closed during the whole respiratory phase. Resulting from this closure, the air contained in the cavity, which cannot be replaced, is gradually absorbed from the cavity, the tension within the cavity decreases and, in consequence, the blood supply to the cavity walls improves and healing results. Obviously in the first place, the stenosis of the bronchus is purely functional, and it only becomes organic when the tuberculous disease has healed, as it usually does by fibrous tissue replacement of the diseased tissue; this latter possibly takes three months.

(3) *Decompression of the cavity* is carried out either by the introduction of a tube into the cavity, after the method of Monaldi, or by open drainage of the cavity, in the same way as for drainage of an acute lung abscess.

Mention should be made of a completely different principle of surgical treatment, that of excisional surgery. Resection of the lung for tuberculosis follows the principle of removal of a diseased area for which other forms of treatment are unsuitable; consequently, at the present time, the indication for such radical measures are relatively clear-cut.

It cannot be stressed too strongly that the treatment of pulmonary tuberculosis is primarily a medical problem, and that surgical intervention is indicated only when medical measures such as bed rest and artificial pneumothorax treatment have either failed or, because of late recognition, are obviously unsuitable. Bed rest, however, should be instituted in every case, so that an assessment can be made of the general condition of the patient, and the phase of his resistance against the disease. This is important, as in a large majority of cases it will be found that periods of stability, in which the patient remains apyrexial, maintains or even gains weight and the sole symptoms are those of cough and sputum, are followed by periods of instability accompanied by toxæmia which is evinced by pyrexia, malaise, loss of weight, increase of cough and sputum, and fluctuations in the blood erythrocyte sedimentation rate. These observations afford an index of the patient's resistance against his disease, both in general and at the time of observation.

In the more serious interventions, especially that of thoracoplasty, it is necessary to operate at the time when the patient's resistance is at its peak, and consequently, it is essential that the whole history and details of the course of the disease, including the serial X-rays and blood examination, are available when the question of treatment arises. The obvious necessity for close cooperation between the physician in charge of the case and the surgeon need not be stressed.

SURGICAL INTERVENTION

The indications for, and contraindications to, pneumothorax treatment are outside the scope of this discussion, but in general, this form of treatment will have been considered and probably tried before surgical intervention is considered. The procedures using the principle of relaxation are as follows: (1) operations on the phrenic nerve inducing paralysis of the diaphragm; (2) extrapleural artificial pneumothorax; (3) thoracoplasty.

PHRENIC INTERRUPTION

Interruption of the phrenic nerve is carried out under local anæsthesia through a small transverse incision in the neck, and when the nerve is identified, with any accessory nerve which may be present, it is crushed with a pair of artery forceps. This produces a paralysis of the homolateral hemidiaphragm which persists, in the large majority of cases, for from six to nine months, when the normal movements return; in a small percentage of cases, 1 to 3 per cent., the paralysis remains permanent. The indications for the operation are as follows:—

(1) Apical cavitation: Cavities at the apex of the upper lobe, which are not more than one inch in diameter, provided there is no serious degree of surrounding infiltration.

(2) In selected cases of apical cavitation in the presence of an artificial pneumothorax, when indivisible apical adhesions are present.

(3) In cases of cavitation of the lower lobe when a satisfactory artificial pneumothorax cannot be established. Only a small percentage of these cases can be dealt with satisfactorily by this method; the large majority can only be dealt with by resection. Despite this, all cases are advisedly treated by the more simple procedure before submitting them to the more severe intervention.

Lastly, diaphragmatic paralysis may be used as an adjuvant to the forms of relaxation therapy. Paralysis of the diaphragm produces its effect mainly by the resultant rise in the hemidiaphragm, which decreases both the size of the pleural cavity and the inspiratory pull of the diaphragm on the diseased area. The ascent of the diaphragm can be increased by the introduction of air into the peritoneal cavity and it is, at present, common practice to combine pneumoperitoneum with phrenic interruption. The operation for interruption of the phrenic nerve is simple, and therein lies danger. It should not be utilized unless there is a reasonable expectation of a good result, for its performance tends to give the patient, and not infrequently his medical attendant, a sense of security, which experience often disproves, and in consequence more suitable measures are often unduly postponed.

EXTRAPLEURAL ARTIFICIAL PNEUMOTHORAX

This operation is carried out when a satisfactory intrapleural artificial pneumothorax cannot be established. The operation is performed most

commonly under local anæsthesia. A segment of the fourth, fifth or six rib is removed and the parietal pleura is stripped, with the underlying lung, from the chest wall, Sibson's fascia, and the mediastinum, in order to obtain complete relaxation of the diseased area of lung. The space thus obtained is maintained by refilling it with air in a manner similar to that used with the intrapleural pneumothorax.

Extrapleural artificial pneumothorax has certain distinct advantages over the more radical procedure of thoracoplasty. First, the bony architecture of the chest remains intact, and in consequence there is no deformity; and, perhaps even more important, the lung is not subject to paradoxical movements in the postoperative stage, as it is of necessity following thoracoplasty when relatively large segments of ribs have been removed. Secondly, relaxation is not necessarily permanent, as in certain cases the pneumothorax can be abandoned after four or five years, although in a large percentage it will be permanent.

There are, however, the following associated disadvantages. First, not all cases are amenable to the procedure; secondly, there is a not inconsiderable risk of infection of the extrapleural space, both tuberculous and pyogenic, although this complication is not as serious as heretofore, owing to the availability of suitable antibiotics. Most of all the patient needs constant skilful supervision, and remains, in every sense, a patient under treatment during the whole period that the pneumothorax is maintained. The latter objection does not obtain with a successful thoracoplasty, which is of necessity a definitive operation and, except for periodic follow-up observations, the patient needs no further intervention.

Extrapleural artificial pneumothorax has a mortality rate which is almost the same as that for thoracoplasty, and the results of the two procedures are comparable. It will be appreciated from the foregoing that cases selected for operation must be chosen carefully, and the best results are obtained in early cases of upper lobe cavitation in which the cavities are not greater than four centimetres in diameter, and in which there is no gross infiltration of the remaining part of the upper lobe. This group forms the ideal indication, but the indications can be extended considerably, according to the experience of the surgeon. Often, however, it is only at the time of operation that a decision can be made as to the feasibility or otherwise of the procedure.

THORACOPLASTY

Thoracoplasty is without doubt the most serious of the relaxation procedures, both from the patient's and the surgeon's point of view, for the following reasons. The standard operation is done in two or more stages; the technique of the operation is more difficult involving as it does a liberation of the apex of the lung, and it inevitably results in a degree of deformity of the chest resulting from the collapse of the bony cage. Lastly, as has already

been indicated, the portion of the lung which has been mobilized is subject to paradoxical respiratory movements in the immediate postoperative phase. This last factor is probably the most important from both the physiological and pathological aspects, in that the disturbance to normal respiration caused by paradoxical movements of the chest wall are similar to those resulting from an open pneumothorax, although not so severe. These movements also favour spread of the disease *via* the bronchial tree, in that during inspiration secretions are aspirated into the normally functioning lung, from the disease area, which deflates during inspiration owing to its lack of support by an intact chest wall. The dangers of paradoxical movement can, however, be minimized by careful staging of the operation, resecting small portions of rib in those cases in which the apex of the lung is soft and mobile, and reserving large resections at each stage for those cases in which the apex is hard and fibrotic. These disadvantages can be overstressed and must be balanced against the very real advantages of the operation. As already stated, the operation, when successful, is definitive, and the patient needs no further treatment; with a well-planned modern operation, only a minimal amount of lung need be collapsed. The degree of deformity is considerably minimized by correct postoperative exercises and is, for practical purposes, quite undetectable when the patient is clothed.

As with all patients suffering from this disease, it is good policy to explain fully to the patient the aims and object of the proposed treatment and to give an outline of the course he will follow. No patient will refuse a thoracoplasty if the position is clearly explained beforehand. Broadly speaking, thoracoplasty, with certain exceptions, is applicable to all cases which cannot be treated effectively by simple means. Whereas heretofore many cases had perforce to be kept at bed rest for many months before operation could be undertaken, and in certain cases even then no active intervention was possible, with modern chemotherapeutic aids even the unstable cases can be so stabilized as to make operative intervention a relatively safe procedure in a fraction of this time.

It would be foolish to suggest that thoracoplasty or any of the relaxation procedures of themselves cure the patient's tuberculosis; in the final analysis it is the patient's own resistance which effects the cure. In consequence, following operation a period of bed rest for at least three months is essential, and after this a course of sanatorium treatment must be instituted in order that exercise can be graduated under medical supervision, and the patient be instructed as to his mode of life and behaviour on his return home.

The results of thoracoplasty are encouraging. The early mortality of the operation, including all categories of the disease and patients of all age-groups, is 10.6 per cent.; the late mortality, 9.9 per cent. The percentage rate of cavity closure, so far as it is possible to assess radiographically and tomographically, and the percentage of conversion of sputum from positive to negative, is 89.5 per cent.

RESULTS OF THORACOPLASTY

Total number of cases (treated in 2 institutions)			518
Early mortality (patients unable to leave hospital)			55 (10.6 per cent.)
Number of cases followed up			421
Cavity closure and sputum negative or no sputum			338 (89.5 per cent.)
Cavity unclosed or sputum positive			41 (10.5 per cent.)
Late mortality: Before 1 year	8		
After 1 year	34		42 (9.9 per cent.)
Cases insufficiently followed up			6
Cases operated on less than 1 year ago			36

MONALDI'S TUBE DRAINAGE

The third principle involving decompression of the cavity by drainage follows the principles originally suggested by Eloesser, who deliberately established open drainage after the principles used in ordinary pyogenic lung abscesses. This method has had a certain vogue, but is not as well favoured in this country as on the Continent. The cavity is laid open and allowed to granulate; any bronchial fistulæ which are present and persist are cauterized with silver nitrate or some other escharotic.

Monaldi first introduced the principle of tube drainage and negative pressure aspiration of the cavity. A tube is inserted into the cavity through a special cannula and left *in situ*, the cavity being subjected to intermittent suction at a negative pressure of about 6 to 8 cm. of water. This method, although very effective in reducing the cavity, takes little cognizance of the underlying bronchial factor. It is right to say that Monaldi has reported considerable success with this method, although workers here have not had the same happy experience. More recently, Maurer and others have combined tube drainage with instillations of streptomycin, for which good results are claimed.

LUNG RESECTION

Lung resection for pulmonary tuberculosis is a more recent addition to the surgical armamentarium and is to a certain extent still *sub judice*, in that long-term results are not yet available for a complete assessment. There are, however, certain tuberculous conditions of the lung which are not amenable to thoracoplasty and for which resection offers the only method of relief and cure. They are:—

(1) Closed tuberculous lesions, which can be subdivided as follows: (a) the so-called tuberculoma, which is a lesion of the interstitial tissue, and is either frankly caseous, or fibro-caseous; (b) a localized tuberculous broncho-stenosis affecting a segment or subsegment of a lobe; and (c) a condition, which on pathological grounds, appears to be a developing primary focus.

(2) Cavities affecting the basal segments of the lower lobes and also those in the middle lobes. Cavities in these positions are notoriously difficult to close by ordinary relaxation procedures, and although the simpler measures of diaphragmatic paralysis and pneumoperitoneum should be tried before

resection is undertaken, the large majority will inevitably need the more radical procedure.

(3) Stenosis of the larger bronchi. This condition is most often associated either with cavitation of the lung or superadded infection behind the stenosis, and consequently forms an ideal indication for resection. Stenosis of the upper lobe bronchus with associated cavitation in that lobe, does not, in my opinion, constitute an indication, as these cases can be treated satisfactorily by thoracoplasty.

(4) Rupture of the cavity into an artificial pneumothorax. This accident carries with it a high mortality when treated by conservative measures of pleural drainage, and without doubt resection is a life-saving measure.

The early mortality of resection is not high, although the complication rate of the operation is not inconsiderable. The late mortality rate has yet to be assessed, and this will not be possible under five or ten years.

RESECTIONS FOR PULMONARY TUBERCULOSIS

Total resections	60
Pneumonectomy	33 (deaths 0 late, 4 early)
Lobectomy	27 (deaths 1 late, 1 early)
Spread:	
Pneumonectomy	3
Lobectomy	2 (1 patient died)
Fistula:	
Pneumonectomy	4
Lobectomy	?1
Empyema:	
Pneumonectomy	6

CONCLUSION

Pulmonary tuberculosis is a disease which can be cured in all but the most advanced cases, even in cases with bilateral disease unless it is very extensive. There is a reasonable hope that the patient may be rehabilitated and be able to live a normal life, although possibly in a more restricted circle than previously. The necessity for close cooperation between the medical attendants, and above all the patient, is paramount, and also for close supervision and care during the years following this treatment. The aim and object of all treatment is the restoration of the patient to as normal a state of health and life as possible, and this goal should be kept clearly before the patient during the whole therapeutic phase. In this way, the patient's morale can be sustained through what inevitably must be a tedious and time-consuming process.

TUBERCULIN AND ITS APPLICATION

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When Koch (1891) first announced the discovery of tuberculin, he considered that he had found a valuable therapeutic agent for the treatment of tuberculosis. The results obtained with this new substance were, however, extremely disappointing and often led to serious consequences for the patient. During these preliminary therapeutic trials with tuberculin, Koch observed severe general and local reactions in some patients. This observation led to the use of tuberculin in 1890 as a diagnostic agent in the form of a subcutaneous test. The patient was first observed at bed rest for several days. Then an injection of tuberculin was given subcutaneously and, if this was followed by a rise of temperature with an increase of signs around the suspected focus, the patient was regarded as suffering from tuberculosis. Later a number of tuberculin tests were described, such as the cutaneous or 'scratch test' of von Pirquet (1907), the conjunctival test of Calmette (1907), the intracutaneous test of Mantoux (1908), the percutaneous test of Moro (1908), the patch test of Vollmer and Goldberger (1937), and the transcutaneous test of Corper (1944). Of all these tests, those of von Pirquet and Mantoux have been most widely applied.

TYPES OF TUBERCULIN

Koch's old tuberculin (O.T.) 1890 was originally prepared from 5 per cent. glycerinated broth on which tubercle bacilli had grown for six to eight weeks.

Cultures together with their media were boiled, strained and filtered. Then the filtrate was concentrated by evaporation to one-tenth of the original volume. This yielded a viscid brown fluid containing several specific products of the tubercle bacilli, as well as concentrated ingredients of the medium. Studies by Long and Seibert (1932, 1935) showed that the active constituent of tuberculin was protein in nature, and could be isolated in a pure form. Various methods were tried until finally it was found that precipitation of the ultrafiltered product with trichloracetic acid yielded a potent product which was stable in its potency for years under suitable conditions. This product was called 'purified protein derivative tuberculin' (P.P.D.), and was found to be specific and satisfactory for skin testing. Later studies on the production of P.P.D. showed that the cumbersome collodion ultrafiltration could be omitted, and that the process of direct precipitation with trichloracetic acid followed by centrifugal washing to remove media constituents and soluble metabolic products could be used. Recently Seibert and Dufour (1948) succeeded in preparing a purer form of tuberculin by using ammonium sulphate at pH 7.0 as precipitant instead of trichloracetic acid. In 1943, Corper and Cohn noted that tuberculin was produced by tubercle bacilli as the result of the action of the autolytic enzymes of the bacilli. This observation led to the production of 'autolytic tuberculin', in which washed viable tubercle bacilli suspended in a watery solution were incubated in sealed glass tubes containing diethyl ether and petroleum. Within about three days the bacilli were destroyed, permitting autolysis to occur with the liberation of

tuberculo-protein within a week. After drying over phosphorus pentoxide *in vacuo*, the tuberculo-protein was pulverized to a fine yellow powder. This autolytic product was found to be biologically identical in activity with tuberculin obtained by growing these bacilli in a non-protein synthetic medium for over three months. This autolysate was free from constituents of the medium as well as foreign material resulting from the growth of the bacilli.

STANDARDIZATION OF TUBERCULIN

One of the earliest methods of standardization was the determination of the minimal lethal dose of tuberculin injected subcutaneously into a tuberculous guinea-pig (Koch, 1891).

The method used at the Veterinary Laboratory of the Ministry of Agriculture at Weybridge (Green, 1946) and most laboratories consists of, first, the determination of the protein nitrogen by Kjeldal's method, and secondly, the biological test on sensitized guinea-pigs and cattle. Eight white guinea-pigs in good condition and weighing over 350 grammes are sensitized by intramuscular injection of 0.5 ml. of live organisms. Three weeks later each animal receives four injections of 0.2 ml. tuberculin, at dilutions 1/500, 1/1000, 1/2000, 1/4000, intradermally into the cropped depilated skin on one side of the vertebral column. On the opposite side at corresponding points four similar injections are given of a standard preparation. Readings are taken at the twenty-fourth and forty-eighth hours and calculations of relative potency are made. Attempts have also been made to use the complement fixation and the precipitin reactions (Dreyer and Vollum, 1924) to determine the strength of tuberculin, but these reactions are not so accurate as the biological methods.

TUBERCULIN REACTIONS

The basis of the tuberculin test rests upon the observation that twenty-eight to seventy days after infection by the tubercle bacillus, a generalized sensitivity of the tissues of the body to the introduction of tuberculin follows. For the purposes of the test, the skin is the tissue selected for demonstrating this reaction. There is no true sensitivity to tuberculin in persons not infected with mycobacteria other than the more immediate temporary reactions in those with anaphylaxis or histamine hypersensitivity, and the delayed atypical non-specific reaction with higher concentrations of tuberculin (Hart, 1932, a, b). It was for this form of tuberculin sensitivity that the term of 'allergy' was originally introduced by von Pirquet in 1907. Various phases of allergy have been recognized, starting with the 'pre-allergic' period, which is the interval between the time of infection and the development of manifest sensitivity. During this period an infra-tuberculin reaction can be observed at the site of an inoculation of dead tubercle bacilli, e.g., 0.1 mg. B.C.G. vaccine killed by heat (De Assis, 1943, 1944). This reaction consists of a nodular infiltration of the skin at least 5 mm. in diameter. The allergic or hypersensitivity phase usually persists to a varying degree throughout life, being maintained or increased by exposure to further infection with tubercle bacilli, and depressed in severe and advanced forms of tuberculosis with marked toxæmia (e.g. miliary, meningitic or moribund cases). This hypersensitivity returns to some extent after treatment with streptomycin (Bernard *et al.*, 1948; Zim, 1949). Hypersensitivity is also depressed by sarcoidosis, and temporarily by such intercurrent infections as measles, scarlet fever and undulant fever.

A more complete list mainly based upon the results obtained with the less sensitive von Pirquet test is given by Hart (1932a). This includes influenza, whooping-cough, varicella and other conditions such as menstruation, pregnancy, lactation, ultra-violet radiation, and during tuberculin therapy. From a study of patients critically ill with diseases other than tuberculosis and histoplasmosis, Furcolow *et al.* (1948) found that critical illness exerted a depressing effect on skin sensitivity to tuberculin and to histoplasmin. Almost half of those insensitive when critically ill reacted positively to skin tests again after they began to improve. The question of 'anergy' due to old age has been raised by Coury and Marland (1948), who found that 6.6 per cent. of 257 inmates of a Parisian home for the aged gave negative reactions to 1:1000 dilution of tuberculin. Similar observations were described by Furcolow *et al.* (1948).

In the early stages of tuberculous disease the tuberculin reaction is strongest, and this persists while encapsulation of the lesion is occurring. Later, hypersensitivity diminishes with time, especially when healing and fibrosis have been followed by death of the bacillus. It has been speculated that two or more years are required for the disappearance of this hypersensitivity after the death of tubercle bacilli. This period depends upon the virulence and survival of the bacilli, the size and activity of the lesion, and the resistance of the host. The minimum period for the persistence of tuberculin sensitivity after a primary infection which heals has been calculated as five to ten years. This is made up from the time taken for bacilli to disappear from the average small tubercle (about two-and-a-half to five years) and the minimum period for persistence of hypersensitivity as observed after B.C.G. vaccination, which is usually three to five years.

In the Prophit Survey 1935-44 (Daniels *et al.*, 1947), it was found that in a certain proportion of persons, spontaneous loss of sensitivity occurred within a year of entry to the survey. This varied from 5 to 6 per cent. in controls, students, and a group of nurses working in hospitals admitting a selective type of patient, to 3.5 per cent. in another group of nurses working in hospitals admitting all types of patients, including chronic and advanced cases of pulmonary tuberculosis. Only 1.5 per cent. of tuberculosis contacts lost their sensitivity. Various other figures are given for loss of tuberculin sensitivity, ranging from 5 per cent. by Opie and McPhedran (1935) to 11 per cent. by Long (1939). In a series of 2,315 originally tuberculin-sensitive children observed for periods of one to seven years by Gillard and LeCoq (1948), 35 per cent. between the ages of four to ten years became negative reactors compared with 9.5 per cent. between eleven to fifteen years of age, and 3.8 per cent. between sixteen and twenty years of age. Loss of sensitivity is not necessarily followed by loss of resistance, although these two factors are often related. This form of hypersensitivity, which is of the cellular type, is not affected by antihistamine drugs or by rutin (Criep, Levine and Aaron, 1949; Friedman and Silverman, 1949). Henderson (1949), however, using larger doses of antihistamine drugs for longer periods, has been able to demonstrate depressed sensitivity to 0.00002 mg. P.P.D. which may last for several weeks following the cessation of the drugs.

Recently, Lawrence (1949) has shown that passive cellular transfer of tuberculin hypersensitivity is possible by the intradermal injection of suspensions of leucocytes obtained from the blood of tuberculin-positive donors.

METHODS OF TUBERCULIN TESTING

In the original *von Pirquet test*, one drop of 25 per cent. old tuberculin and one drop of control were placed on the cleansed skin of the forearm, and a scratch made through each drop. A red papule more than 5 mm.

in diameter developing after forty-eight hours was regarded as positive. This test was modified by Morland (1912) to obtain quantitative results by using different strengths of tuberculin.

The Mantoux test.—The most commonly used test in Great Britain at the present time is the intracutaneous or Mantoux test.

The tuberculin used is produced on synthetic medium in a similar way to Koch's O.T. and is known as O.T. H.C.S.M. (heat-concentrated synthetic medium). For the preparation of the various dilutions of O.T. the Prophit Survey used a special borate buffer solution. The dilutions were stable for one month when kept at 4°C. (40° F.). The doses which can be used are:—

0.1 ml. of 1:100,000 Old Tuberculin T. (human) corresponding to 0.001 mg. O.T.
0.1 ml. of 1:10,000 ,, ,, ,, ,, corresponding to 0.01 mg. O.T.
0.1 ml. of 1:1,000 ,, ,, ,, ,, corresponding to 0.1 mg. O.T.
0.1 ml. of 1:100 ,, ,, ,, ,, corresponding to 1.0 mg. O.T.

For practical purposes most workers start with 0.1 ml. of a 1:10,000 dilution, unless the possibility of marked hypersensitivity is suspected. A separate sterile 1 ml. syringe graduated in tenths of a ml. is used for each dilution. Platinum needles of S.W.G. 16 or 18, and length ½ to 1 inch, are found most convenient if available, in that they can be flamed on the syringe in between tests and thus save time (Prophit Survey: Daniels *et al.*, 1947). The flexor surface of the forearm two inches below the bend of the elbow is cleansed with spirit, and the needle is introduced intradermally, parallel to the surface for about ½ inch. The injection of 0.1 ml. should produce a white weal about 7 mm. in diameter (which is the only evidence that the injection has been intradermal). The test is read after forty-eight to seventy-two hours, and the reaction can be measured according to the diameter of the infiltrating œdema produced in the skin. This infiltration can best be seen when the elbow is held slightly flexed, and observed from an oblique angle. Reading of skin tests is as follows (Aronson, 1934):—

Erythema, and œdema more than 5 mm. but less than 10 mm. = +
,, ,, ,, ,, ,, 10 mm. ,, ,, ,, 20 mm. = ++
,, ,, ,, ,, ,, 20 mm. or more = +++
Marked erythema and œdema with an area of necrosis = ++++
Erythema more than 8 mm. alone or œdema less than 5 mm. = doubtful ±
Erythema less than 8 mm. or no œdema = negative o

Adults negative to a freshly prepared dilution of 1:10,000 can usually be retested immediately with a 1:100 dilution, but those giving doubtful reactions should next be tested with a 1:1000 dilution, and then 1:100 if negative to the latter dilution. In children it is safer to use gradually increasing strengths, starting with 1:10,000.

An interesting feature of the Mantoux test is the delayed appearance of a reaction at the site of the test some weeks or months later. This is probably due to the patient having been infected near the time of testing (Daniels, 1943; Thompson, 1949).

Protein Purified Derivative (P.P.D.) may be obtained in 0.002 mg. tablets (or dried powder in ampoules) which are dissolved in 1 ml. of diluent (a buffered salt solution at pH 7.4), so that 0.1 ml. contains the first test dose, 0.00002 mg. equivalent to 1:10,000 to 1:50,000 O.T. (0.01 mg. to 0.002 mg.). For the second strength 0.05 mg. tablets similarly dissolved to give a test dose of 0.005 mg. in 0.1 ml. is equivalent to 1:100 O.T. The W.H.O. Sub-Committee on Biological Standardization has accepted that one Tuberculin Unit (T.U.) is equal to 0.01 mg. International Standard Old Tuberculin (O.T.), or 0.00002 mg. International Standard Reference Preparation of Purified Protein Derivative (P.P.D.) (Holm, 1948). The reading of the results is similar to the Mantoux test with O.T. In order to exclude non-specific reactions from the use of P.P.D 2 (second strength) Furcolow *et al.* (1941) suggested an intermediate P.P.D. dosage of 0.0001 mg. In recent attempts to find a suitable dose of tuberculin for single dose testing, 0.0002 mg. in 0.1 ml. has been found

to give 94.3 per cent. of all possible reactions to the 0.005 mg. dose, with only 4.6 per cent. of severe reactions (++++) (Kuang-Yuan Liu *et al.*, 1949).

In carrying out the test, care must be taken that the needle and syringe are dry and quite free from antiseptics such as spirit or other chemicals which may damage the P.P.D The solutions should be used soon after preparation, because deterioration rapidly occurs with dilution. In making up the solution the resultant mixture should be allowed to stand for two to three minutes, and then be shaken gently. A slight amount of insoluble material which may develop can be ignored without affecting the potency of the solution. The dried P.P.D. keeps for several years without deterioration in potency in a cool dry place. P.P.D. is chiefly used in the U.S.A. and Australia.

Sometimes quite severe reactions develop at the site of the injection which may be followed by necrosis. It has been found that cold applications to the indurated site help to avert these complications (Pilcher, 1944).

Patch tests.—When quantitative tests are not required, or there is an objection to the use of the needle, for example, with children, there are a number of contact tests which can be used. For the Vollmer patch test old tuberculin is impregnated into the centre of a length of adhesive plaster which is closely applied to the skin of the back. In the tuberculin patch test (Evans) small squares of filter paper saturated with a solution of human or bovine Tuberculin Purified Protein (equivalent to 0.09 ml. O.T.) and synthetic medium (as a control) are applied to the cleansed skin and are covered by a piece of adhesive plaster for forty-eight hours. The moisture of the skin dissolves the tuberculin, which is absorbed by the skin and, if positive, produces a sharply defined indurated red square with a lichenoid or follicular elevation. The area under the control should remain pale. The plaster must be applied closely to the skin away from the creases, and not allowed to get wet.

Tuberculin jelly used for *contact tests* consists of 95 per cent. old tuberculin and 5 per cent. adhesive. A suitable preparation has been produced by Allen and Hanburys, London.

The skin between the upper angles of the scapulæ is cleansed with ether or acetone, and one cm. lengths of test jelly are squeezed on to the skin in the form of a 'V', with a similar amount of control jelly as a vertical line two cm. above. Each is covered by a piece of plaster or transparent adhesive plastic, 1.5 cm. square. The patient is then instructed to avoid getting the test wet. After forty-eight hours the plaster is removed and the site kept under observation for one week; any reaction in the form of erythema and at least four vesicles on the site of the 'V' is regarded as positive.

In the Corper (1944) *transdermal test*, autolytic tuberculin is powdered and incorporated into a non-irritating (and non-allergizing), transparent, liquid preparation, which is stable for at least four months at room temperature.

The mixture is painted on the cleansed skin of the forearm by means of a glass rod, and is allowed to dry (usually taking about 2 minutes). The site must be kept dry and the test read forty-eight hours later. Positive readings vary from one or more pin-point, papular, erythematous areas without œdema to an erythematous

area 10 × 30 mm. with œdema extending slightly beyond it. Complete absence of erythema is regarded as a negative reaction. In a series of 64 tuberculous patients, Corper (1944) found 90 per cent. positive reactions to the transdermal test compared with 96 per cent. to intradermal tests. Lawrence (1946) found that this test compared favourably with 0.0002 mg. of P.P.D., but did not think it reliable enough for general use at its present stage of development. It was suggested that a finer suspension of tuberculin would give better contact and more reliable results. Wiley-Jones *et al.* (1949) noted that repeated application of Corper's autolytic tuberculin did not produce any hypersensitivity to this product.

The jelly tests have been found to be slightly superior to the Vollmer patch tests, which become dry and less effective with storage. In a series of Mantoux-positive (1:1000) children, 80 per cent. reacted positively with the Vollmer patch and 87 per cent. with the jelly test (Deane, 1946). When the skin had been previously abraded by rubbing lightly with fine sandpaper (cabinet makers' No. 0) without causing erythema, Deane obtained positive reactions with the jelly in 100 per cent. of cases. When there is any doubt about the result, these contact tests are best followed up by intradermal tests.

EVALUATION OF THE TEST

The significance of a positive test depends upon a number of factors, including age, results of previous tests, a history of contact, clinical history and findings, radiological appearances, and the results of other ancillary tests.

In children, the tuberculin test is very important and, if positive, the younger the child the more chance there is of the lesion being recent and active. A positive test below the age of one year means that recent tuberculous infection has occurred which is most likely active. Below two years of age the infection is probably active. The time of onset can sometimes be fixed by the knowledge of a history of recent contact or an unexplained pyrexial illness, especially if it is known that the child was previously tuberculin-negative. A history of erythema nodosum, phlyctenular conjunctivitis or pleurisy is also a time indicator. Confirmatory evidence is supplied by finding abnormal physical signs or radiological changes in the chest, and tubercle bacilli in the gastric washings or stools. From two to five years a positive test cannot be used to indicate active disease without a knowledge of recent contact or an attack of erythema nodosum, or previously negative skin tests. In such cases more stress must be placed upon persistent symptoms, radiological appearances, E.S.R. (erythrocyte sedimentation rate), and the demonstration of tubercle bacilli in the various secretions. Over the age of five years a positive test means that tuberculous infection has taken place, but here again it is not possible to determine the age of the lesion without a knowledge of a history of recent contact or previously negative skin tests. To determine the degree of activity at this stage, clinical and radiological observation is essential, and this must be supplemented by a careful search for the tubercle bacillus. Griffith (1930) states that as a general rule high tuberculin sensitiveness and active disease go together. Marked reactions favour, but do not prove, active disease. It must be remembered that strong skin reactions are sometimes obtained in rheuma-

toid arthritis and asthma (Urbach and Gottlieb, 1946) which are not necessarily specific evidence that the condition is tuberculous, and are regarded as metallergic reactions. Sweany (1947) has claimed that in patients with demonstrable clinical or radiological disease in the chest, 91 per cent. positive to 1:10,000 O.T. were found to have 'significant' tuberculosis. There was a known error of 0.5 per cent. and about 2 per cent. of diagnostic failures. A pulmonary or bone lesion with a negative skin test carried to a 1:100 dilution O.T. is unlikely to be tuberculous, if the previous conditions which depress tuberculin sensitivity can be excluded. In the case of calcified pulmonary lesions with negative tuberculin tests, intradermal tests with 1:100 coccidioidin or 1:100 histoplasmin should be carried out where these conditions are endemic.

In a series of cases of tuberculous pleurisy with effusion, Karron and Purves (1947) found that 79 per cent. were positive to skin tests with the first strength of P.P.D., and the rest were positive to the second strength. There was no exacerbation of the pleurisy after the test. A modified form of test is used in skin tuberculosis when tuberculin is injected into the periphery of the suspected lesion. If a stronger reaction is produced by this means than with a similar injection into a normal area of skin, this result can be taken as useful evidence in favour of the tuberculous nature of the skin lesion (Urbach and Gottlieb, 1946). Another valuable use of the tuberculin test is in the differentiation of avian from mammalian types of tuberculous infection. In the former there is a specific reaction to avian tuberculin which can be regarded as strong evidence if positive. There is no method of differentiating human from bovine infection by skin tests.

Other uses for the tuberculin tests include case-finding surveys of tuberculous infection in infants and children. At the same time this acts as a pointer to the presence of an infecting source in the home or school. Another use is in epidemiological surveys and screenings of the population for further investigation, especially in conjunction with mass X-ray examinations. In choosing nurses and personnel for work on tuberculosis wards in general hospitals or in chest hospitals, sanatoria and laboratories, the tuberculin test should be carried out as a routine investigation. Negative reactors have been found to be more liable to serious tuberculous infection than positive reactors. As a preliminary to B.C.G. vaccination, skin testing is absolutely essential. The best tuberculin test material to adopt before vaccination is still under consideration.

Birkhaug (1949) has observed that the reactions with O.T. after B.C.G. vaccination are sharply raised, markedly œdematous and usually of (++) or (+++) intensity, whereas with P.P.D they are usually flat, poorly demarcated and only slightly indurated. In a group of 20 employees in his division vaccinated with B.C.G. and tested with tuberculin ten to seventeen months later, 100 per cent. gave positive reactions to 0.1 mg. O.T. and only 56 per cent. were positive to a simultaneous test with 0.0002 mg. P.P.D. Some workers have claimed better results with tuberculin derived from B.C.G., but Birkhaug (1949) finds that there is no difference whether O.T. is derived from pathogenic strains or non-pathogenic. Ustvedt has used a 20 mg./ml. suspension of B.C.G. or a 50 mg./ml. of dead

B.C.G. applied to the skin, through which two punctures were made. He obtained a positive reaction in 74 out of 79 cases which had remained negative to O.T. after vaccination (Irvine, 1949).

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ENURESIS IN CHILDHOOD

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At least one child in every twenty fails to attain control of micturition by the age of five years. Normally the child should be dry by day as well as by night considerably before his third birthday, and when this does not occur, the condition is termed 'enuresis'. Most children who suffer from this distressing symptom gradually acquire control of their bladders before they reach adult life, but this recovery is by no means universal.

Although enuresis is seldom caused by serious organic disease, it is a source of much unhappiness both to the patient and to his parents. It is almost the only symptom which children are ashamed of. The child hates the condition and is unwilling to talk about it before strangers. Moreover, he frequently lacks the sympathy and support which he needs from his parents, who more often than not administer severe punishment which nowadays tends to be mental rather than physical. So many parents adopt an attitude of hopelessness accompanied by nagging, that the child becomes morose and introverted, and lives his life sodden, sore, stinking and miserable.

CAUSAL FACTORS

Few conditions have been more misunderstood. The root of most of the mistakes is the tendency to regard enuresis as a disease rather than as a symptom, and consequently to attribute it to one cause. Anyone who studies a large number of cases must be struck by the wide variety of abnormalities encountered. In treating a case of enuresis, it is therefore essential to realize that it is a symptom which may have many causes, and the one that is operating in the individual patient must be sought for diligently. So often the practitioner has persuaded himself that all enuresis is due to one abnormality and proceeds to treat the condition on these lines by measures varying from circumcision to psychoanalysis, without either taking a careful history or examining the patient thoroughly. Or else the mother is told, most unforgivably, that nothing can be done for it, and that she must wait until spontaneous cure sets in—and the child is sent away with the sentence ringing in his ears that he is to remain indefinitely in his wretched state.

The numerous theories put forward about the cause of the condition fall into two groups: those which postulate an abnormal emotional state in the patient which he expresses by wetting himself, and those which account for it as the result of some anatomical or physiological peculiarity. The psychologists tell us that enuresis is either a protest against authority, or that it affords a gratification of libido comparable to masturbation, or that it is a partial return to the infantile state, i.e., a regression. There are serious

objections to all these conceptions. Enuretics are as a rule not rebellious children, indeed they are usually docile, affectionate, and charming until they have had their personalities warped by unjust punishment. It is difficult to see how micturition can afford any gratification of libido in a child of ten to fourteen years of age, as we are told that the excretory phase of infantile sexuality is over by the end of the second year. The theory of regression is more plausible, as many enuretics are shy and timid and appear to find the battle of life too strenuous, but this may be the result rather than the cause of their enuresis, and it is striking how seldom other evidence of regression, such as encopresis, is encountered. Finally, there are two facts which are incompatible with the psychogenic theory of enuresis. One is that the great majority of cases are congenital, and the other is that hypnosis often fails to cure the condition.

Nevertheless, no one can deny that emotional strain plays a great part in the production and maintenance of enuresis. As in so many other apparently organic conditions, psychic factors are of great importance, even if they are not the only or even the major cause. The following case illustrates this:—

Ann C., aged nine, was a lifelong enuretic. She passed urine every half hour. Play therapy under a well-known psychologist had produced no improvement. Treatment on the lines indicated on page 279 made her quite dry for a month without treatment. Then divorce proceedings were opened by the parents, and the patient immediately relapsed. She was again taken to the psychologist who first treated her, but had only made a partial recovery four months later.

On the other hand, many observers have reported the finding of *abnormalities of the lower urinary tract* in enuretics. Winsbury-White (1941) found that over half the female patients had vulvitis, that the majority of males had some degree of stenosis of the urethra, and most of them had small meati. It is well known that spina bifida of any serious degree is apt to cause paralysis of the bladder with dribbling incontinence. Some observers are impressed by the frequency of spina bifida occulta in enuretics, and undoubtedly it is a condition which is often observed, but Morrison (1927, 1944) has shown that this minor malformation is even more common among normal people than in those who wet their beds. Twistington Higgins (1944) considers that 1 in 10 cases are organic, and he often finds urethrotrigonitis. Ellison Nash (1947) believes that adhesions round the corona, by causing gaping of the urethra and allowing the mucous membrane to come into contact with the clothes, may cause reflex micturition. This explanation is doubtful, as usually the glans is completely covered by the prepuce in young boys, even during erection. However, I agree with him that separation of coronal adhesions sometimes materially helps in the cure, as the following case seems to show:—

Kay T., aged 11, was a congenital nocturnal enuretic with frequency and precipitancy in the daytime. He was well adjusted psychologically, being rather an aggressive extrovert. The only abnormal physical findings were coronal adhesions. Ephedrine and thorough waking for micturition at night cut down the wet beds to one a week. The adhesions were then broken down and he remained quite dry without further treatment.

Considering how many medical men are influenced by the mythical effects of phimosis it is remarkable that very few observers regard it as having any influence on enuresis. Probably this is because circumcision neither prevents nor cures the condition. However, Batty (1948) finds that the operation sometimes effects a cure. Probably this is due to the destruction of coronal adhesions.

Physiological abnormalities without anatomical lesions are often found. A hundred years ago Trousseau observed that enuretic patients slept very deeply. Cameron (1946) considers this to be due to ketosis which can be abolished by giving glucose. Smellie (1949) believes that weakness of the internal sphincter is sometimes important and suggests the administration of ergot. He also emphasizes the frequency of nocturnal polyuria, which Batty considers is cured by ephedrine. But, as Campbell (1937) has pointed out, normal children will wake up and micturate whenever the bladder is full, so that increased secretion of urine at night, although it may be an aggravating factor, cannot be considered to be a cause. Many children fill their bladders soon after lying down, and this may be due to the accumulation of fluid in the lower half of the body while they are vertical during the day. This is probably the reason why many children with enuresis wet their beds during the first hour or two of sleep. Infection with threadworms has been regarded as a contributory cause of enuresis, and Batty (1948) finds them present in 31 per cent. of cases. But as threadworms are present in at least 60 per cent. of normal children, their influence cannot be great. Dott (1947) suggests that enuresis is usually produced by failure to empty the bladder completely during the day, but, in my experience and in that of many others, residual urine is not common in enuretics. Campbell finds that trigonitis, posterior urethritis, seminal vesiculitis, prostatitis, and inflammation of the verumontanum are all common, and he thinks that these conditions are caused by masturbation. It is doubtful, however, if children with enuresis masturbate more often than others. Trigonitis, however, may account for those cases in which the wetting only occurs when the patient sleeps on his back.

Of other factors which may operate, mention must be made of faulty bladder training during the day, allergy, infected tonsils and adenoids, and infection of the urinary tract. Epilepsy is usually accompanied by involuntary micturition, and its presence must be eliminated before treating a patient on other lines. Diabetes mellitus or insipidus must be ruled out.

For the purposes of treatment, it is highly desirable to discover any common factors which can be eliminated, and for this purpose I shall give the analysis of 81 cases in children from four to thirteen years which have come under my care in the last five years: 51 of these were private patients, and the others were the first 30 patients coming to the Enuresis Clinic at Leicester in 1946. From these, and from about 150 other patients who have since come to the Clinic, I have reached certain conclusions as to treatment, an account of which is given at the end of this article.

ETIOLOGY AND SYMPTOMS

Family history.—In 24 of the 81 children there was a family history of enuresis. Fifty-three were boys and 28 were girls. Most observers have noted this preponderance of males but Batty (1948) finds that it is more common in girls, except among evacuees, and Sheldon (1944) finds that the sexes are equally affected in younger children. The children come from all grades of society, but cultured parents take the condition more seriously. Enuresis was congenital in 61, and acquired in 18. It was nocturnal in 80, diurnal as well as nocturnal in 28, and diurnal only in 1. Frequency was noted in 60 children; precipitancy of micturition in 50. Dysuria was complained of by only 7 children, all of whom were private patients. Deep sleep was observed by the parents in 54 of the children. The sleep is remarkably profound. Trousseau's original description is: 'The patient informed me that her sleep was deepest towards morning. It was then so profound that it was exceedingly difficult to awake her. When loudly called or well shaken she neither heard nor felt anything; and when compelled to get out of bed she still seemed to be asleep when on her legs'. Allergic symptoms were reported in 8 cases: asthma in 2, asthma and eczema in 1, eczema in 1, urticaria in 2, hay fever in 2.

Psychological examination.—Perhaps the most striking thing about this is that in 29 of the children no psychological abnormality at all was found. They were happy, intelligent children, secure in their home surroundings, doing well at school, reasonably extroverted, interested in hobbies, good mixers, and had satisfactory opportunities of privacy. There is no justification for the allegation that children who wet themselves are mentally dull.

CLINICAL FINDINGS

The *general condition* was usually good, but 10 children were noted to be thin and 5 unduly fat. Evidence of *nasopharyngeal infection* was forthcoming in 18 cases. The *cardiovascular system* showed very few abnormalities but many children had slow pulses—28 had rates of less than 90 per minute. The blood pressure was taken in 36 cases; the systolic reading was between 90 and 110 mm. Hg in 25, below 90 in 4, and above 110 in 7. Abnormalities of the *external genital organs* were very common. Only 13 children were quite normal in this respect. *Circumcision* had been performed on 22 of the 53 boys, or 41.5 per cent. A control group of 200 boys without enuresis had a circumcision rate of only 29 per cent. This suggests that circumcision may predispose to enuresis, but it may only indicate over-anxious parents. Two of the boys had undergone circumcision in the unfulfilled hope that it would cure their enuresis. Of the 31 uncircumcised boys, 18 had *coronal adhesions*. *Hypospadias* was present in 2 boys, *urethral stricture* in 3, *meatal stenosis* in 3, *meatitis* in 3, *balanitis* in 1, and *phimosis* in 1. Twenty of the 28 girls had *vulvitis;* but this may have been the result of the enuresis. One had *vulvovaginitis*, and 1 *adhesions round the clitoris*. Five children had a *urinary infection*.

Rectal examination in 48 cases was normal in only 12. In 27 large amounts of *fæces were present* without any desire to defæcate; 6 had a *tight sphincter*, and 3 of the boys had definite *prostatic tenderness*.

Cystometry was performed in 39 cases (fig 1).

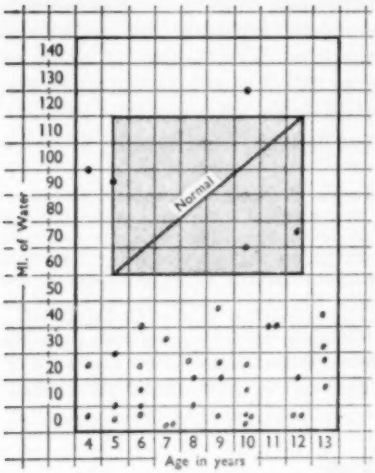

FIG. 1.—Cystometry in enuresis, showing the amount of water injected into the bladder which produced a desire to micturate.

The patient was catheterized, the bladder emptied, and sterile water was instilled, usually in 20 ml. units. The point at which the first desire to micturate was felt was recorded. Campbell states that this normally occurs in children of five to twelve years of age when 60 to 120 ml. have been injected. He found that one-half of the enuretic children showed normal results. Of these 39 children only 4 were normal. All the others but one felt bladder contractions well below the usual level: 13 complained of an intense desire to micturate almost immediately water was introduced into the bladder. Even in those who gave normal readings, once the desire to micturate appeared the whole bladder contracted violently, often expelling the catheter. The one patient who showed the abnormally high reading of 130 ml. had a low intelligence quotient and did not feel any desire to micturate but expelled the catheter and bladder contents when this level was reached. Complete cystometry should also include a record of intravesical pressure, and this has been done in 4 children not included in this series. They all were conscious of bladder contractions at the usual pressure—15 to 20 ml. of water—but at a volume considerably below the normal.

It thus appears that enuretic children's bladders contract at a normal pressure but at a low level of volume. Ellison Nash (1947) finds that some enuretics show uninhibited bladder contractions with both high and low tension types of bladder, and that these contractions occur without any conscious desire to micturate.

Residual urine was measured in only 6 of these cases and it was present in 2. It has been looked for in many subsequent cases, but it is only occasionally found. *Cystograms* were taken in the first 14 of the clinic children, and showed no abnormality. There was no radiological evidence in any case of fluid remaining in the bladder after micturition.

Vesical calculus is unusual. There was no evidence of stone in any of these cases, but I have once seen a child whose enuresis was accompanied by a stone in the bladder.

Spina bifida occulta was present in 6 of the 30 clinic children. This is about the incidence in normal people.

DISCUSSION

It appears from the above review of an admittedly small number of cases

that enuresis is part of a syndrome characterized by marked frequency and precipitancy of micturition, and in purely nocturnal cases by an extreme depth of sleep. Examination reveals a high proportion of abnormalities, either structural or inflammatory, of the external genitalia. Cystometry shows that a few millilitres of water will produce a sufficient rise of pressure in the bladder to cause a desire to micturate. Moreover, the majority of patients go about with a full rectum, the nervous connexions of which are closely associated with those of the bladder. Lastly, psychological anomalies, although apparently important in some cases, are often trivial or absent.

In considering the significance of these findings, it is necessary to review briefly the mechanism of micturition.

The muscular coat of the bladder, known as the detrusor, is composed of an outer longitudinal layer; a middle circular layer, most marked at the base, where it forms the internal sphincter; and a thin, inner longitudinal layer. The muscle is unstriped, except in the lower part of the sphincter and in the trigone, which is a triangular sheet between the ureteral orifices and that of the urethra. This passes through the sphincter to the floor of the proximal urethra. The latter is further surrounded by the striped muscles of the bulbo-spongiosus and sphincter urethri. Normally, intravesical pressure is kept constant at 15 ml. of water. As more urine passes into the organ the detrusor relaxes, and normal pressure is maintained. There comes a time, however, when the detrusor fails to relax and the pressure rises, and when it reaches

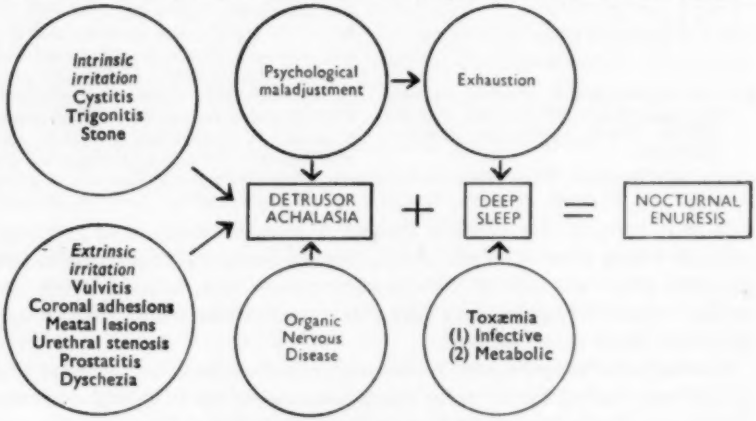

FIG. 2.—The pathogenesis of nocturnal enuresis.

18 ml. of water, the individual experiences a desire to micturate. Rhythmic contractions now take place, but impulses from the higher centres *via* the sympathetic cause further relaxation of the detrusor and the desire passes off temporarily. When a convenient opportunity presents itself, intra-abdominal pressure is voluntarily raised by closure of the glottis and forcible descent of the diaphragm, intravesical pressure is raised to 30 to 40 ml. of water, the sphincter relaxes, and a few drops of urine are expelled into the urethra. This causes a mass reflex contraction of the detrusor, and the bladder is emptied. The trigone, by its contraction, pulls the urethra into line with the bladder and forms a channel leading through the sphincter into the urethra.

The nervous control of this mechanism is supplied by the sympathetic and parasympathetic. The parasympathetic pelvic nerves come from the

1st, 2nd and 3rd sacral segments and cause contraction of the detrusor and relaxation of the sphincter. The sympathetic fibres run in the ilio-hypogastric nerves from the 1st and 2nd lumbar segments, and reduce the tone of the detrusor, but cause contraction of the sphincter. What anomaly in this mechanism can produce the syndrome described? Surely the answer is failure of the detrusor to relax.

In 1915, Hurst put forward the suggestion that the condition known as cardiospasm was due to failure of the cardiac sphincter of the œsophagus to relax, a condition for which Perry coined the word 'achalasia'. Later the term was applied to other sphincters of the alimentary canal. I suggest that enuresis is fundamentally an achalasia, not of a sphincter, but of the whole detrusor muscle. This would explain the associated symptoms of frequency and precipitancy. It accounts for the low readings obtained by cystometry. A full rectum, peripheral irritation, stenosis of the urinary passages, may all reflexly cause an excessive tonus in the vesicle muscle. Psychological factors too, are known to have an important influence on the tone of unstriped muscles. Detrusor achalasia alone would produce frequency, urgency, and sometimes diurnal enuresis. When excessively deep sleep is added, the familiar picture of enuresis occurring almost immediately the patient falls asleep is produced (fig. 2).

TREATMENT

If detrusor achalasia and deep sleep together produce nocturnal enuresis, the indications for treatment are clear. If these can be prevented the enuresis will be cured. For this reason drugs which stimulate the sympathetic and inhibit the cranio-sacral nerves may be expected to be beneficial, and the popularity of ephedrine and belladonna in the treatment of enuresis is thus explained. But in addition to this it is usually desirable to combat the profound slumber which is so often present, and for this, amphetamine is indicated. It is remarkable how large a dose can be taken by an enuretic child without producing sleeplessness. Whereas a normal adult will be kept awake until the small hours by 5 mg. taken at 7 p.m., many enuretic children will sleep profoundly after taking 15 to 20 mg. at bedtime.

But before embarking on a course of drug treatment, simpler measures should be tried, and these alone will be found to be successful in some cases. Local abnormalities should be rectified. Increasing the intervals between the acts of micturition during the day will force the detrusor to relax. The keeping of a calendar on which successful nights are marked by coloured stars, with a substantial reward for a dry week, will help the child to concentrate on the successes rather than the failures. The abrogation of all punishment, corporal or mental, is of paramount importance. The child should also be trained to have the bowels thoroughly opened before retiring. He should be allowed to read or play in bed for half an hour before settling for the night, and then made to micturate, so that the excess of fluid which has accumulated in the lower limbs during the day will be excreted before sleep. The

child should be thoroughly wakened for micturition before wetting occurs. So many parents 'lift' their children and make them micturate in their sleep, thus teaching them to perform the very act they are trying to prevent.

If both management and drugs fail to cure, good results may sometimes be obtained by graduated distension of the bladder to the limit of tolerance once a week. If success still eludes one, hypnosis may be tried. As a rule it is very easy to hypnotize children, and sometimes they can be induced to wake up for micturition by this means. But a word of warning is necessary. Some children like being hypnotized, and one inveterate bedwetter told me while in the hypnotic state that he continued to wet his bed so that he could go on being hypnotized! If all these measures fail, the child should be referred to a urologist for complete investigation under anæsthesia.

The following scheme of treatment is undertaken at the Leicester Enuresis Clinic:—

Stage I. Thorough wakening for micturition when parents retire.
Calendar.
Increase intervals between diurnal acts of micturition.
Defæcation at bedtime.
Reading in bed for half an hour before sleep.
Correction of obvious physical and psychological defects.

Of 55 children who had this treatment alone, 6 were cured, 8 were greatly improved (more than five dry nights a week), 19 were improved (the amount of wetting was reduced and dry nights amounted to from one to four a week), and 22 were unaffected. (Many of the private patients were brought for one consultation only and the results of treatment are not accurately known.)

Stage II: Drugs.—Belladonna and amphetamine. Dosage must be adequate. A child of seven years will usually require tincture of belladonna, 10 minims (0.6 ml.) twice a day, and 15 minims (0.9 ml.) at night. This dose must be attained gradually, and watch must be kept for dryness of the mouth, difficulty in visual accommodation, and tachycardia. Five mg. of amphetamine are given at night at first, and the dose increased until the child wakes easily.

Nine children were cured by these means, 9 were greatly improved, 19 improved and 17 were unaffected.

Methyl ephedrine, ¾ of a grain (45 mg.) for a child of five, or ephedrine, ½ a grain (32 mg.), was given to 9 children: 3 of them were cured, 2 greatly improved, 1 improved and 3 were unaffected.

Stage III; Distension of bladder

Of 16 children, 2 were cured, 3 were greatly improved, 5 improved and 6 showed no change.

Stage IV; Hypnosis

Twenty-one children were treated by hypnosis: 5 were cured, 5 greatly improved, 6 improved, and 5 were unaffected.

Other methods employed for certain cases were:—

(1) *Bobbin* tied to back for children who only wet their beds when sleeping on their backs: 1 cured, 1 greatly improved, 1 improved.

(2) *Methyl testosterone*, 10 mg. daily: 1 cured, 1 improved, 1 unaffected.

(3) *Dilatation of stricture.*—Three boys have had strictures dilated. In all

cases they were dry so long as the dysuria produced by their operation lasted —after which they all relapsed.

(4) *Referred to psychologist.*—Five children: 1 showed some improvement.

Relapses are common. As Batty (1948) points out, it is easy to cure enuresis in the summer, and no child should be considered cured until he has had a dry winter. Apart from this, Browne and Ford-Smith (1941) have pointed out that enuresis is often a cyclical disease, and spontaneous remissions may occur. Relapses account for some cases being listed as cured by one method, and then coming again and being cured either temporarily or permanently by another. Of the 55 children in whom the results have been given here, 23 were permanently cured, 8 were unaffected, and the others improved to a greater or less degree. Many of the last were almost cured—they would have a slight accident once or twice a week only.

Once the condition is under control, it is as well to adopt the procedure recommended by an anonymous sufferer in 1949. If for any reason she expects to sleep deeply, she takes ephedrine at night. Personally I think that methyl ephedrine is more effective.

Finally, I must state that when I began to take a special interest in enuresis eight years ago, I expected to have to deal with a psychological problem. As things have turned out, I have found myself faced with a physical one, although emotional factors play a large part in maintaining the symptoms.

SUMMARY

(1) Enuresis is a symptom of many conditions.

(2) It is often familial.

(3) Concomitant symptoms and physical findings point to achalasia of the detrusor and deep sleep being the fundamental lesions.

(4) Psychological factors are of only secondary importance.

(5) Treatment must be directed towards relieving the abnormality of bladder tone and the lightening of sleep.

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GASTRO-DUODENECTOMY

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Many articles have been published recently on the aftermath of gastrectomy for duodenal or gastric ulcer, and special mention has been made of digestive disturbances, particularly that sequence of post-cibal events alluded to collectively as the 'dumping syndrome'. The clinical symptoms apparently vary in severity. The main feature of this syndrome is upper abdominal distension coming on shortly after meals, accompanied by a feeling of drowsiness and lassitude. Nausea and vomiting occasionally occur, whilst cold sweats, flushing of the head and face, palpitations, and intestinal borborygmi may be experienced.

The incidence of these symptoms is variously stated, but in certain cases they may persist to such a degree as to create a definite physical disability, making life a burden and preventing the patient from resuming gainful employment. In others, in the immediate postoperative period, the afferent loop is slow to empty: an uncomfortable distension occurs, and convalescence is unduly prolonged. A number of patients who may experience only a minor degree of post-cibal discomfort, attempt to correct it by undereating, resulting in failure to gain weight and inability to return to that feeling of good health which they were promised before operation.

CAUSAL FACTORS

The consensus of opinion today indicates that the following mechanisms, singly or collectively, are responsible:—(1) The newly created gastric remnant emptying rapidly into the efferent loop causes a sudden distension of the jejunum. (2) Some of the rapidly evacuated gastric contents escapes into the afferent loop causing an obstructive distension of the blind duodenojejunal segment. Similarly, the afferent loop may become uncomfortably distended with bile and duodenal secretion if its outlet is impaired mechanically by faulty technique. (3) The rapid emptying into the upper jejunum results in hyperglycæmia. This in turn causes a reactive hypersecretion of insulin and subsequent hypoglycæmia. This is, however, now believed to be a relatively unimportant cause of post-cibal distress.

RELATIONSHIP OF THE OCCURRENCE OF SYMPTOMS TO OPERATIVE TECHNIQUE

That there is a definite relationship between the occurrence of symptoms and the technique adopted, seems to be well substantiated by a perusal of certain published series of cases.

Muir (1949-50), in an excellent review of the whole subject based on personal observations of 124 gastrectomies, found that 75 per cent. 'suffered from symptoms of dumping syndrome at some time'. Of these 124 cases, 92 had an antecolic type of anastomosis with a full-width stoma, and the remainder a retrocolic. Mimpriss and Birt (1948), comparing the functional results in differing types of technique, came to certain conclusions. They state that in the antecolic type of anastomosis, in which the afferent loop was attached to the greater curvature, most patients 'complained of side-effects for some months after operation', and attribute this to a proximal loop filling. On the other hand, in the operations in which a retrocolic anastomosis had been performed, the immediate postoperative course was satisfactory, and the average final result was classified as good. Lake (1948), presenting a personal series of 615 cases, reports post-cibal syndromes in only 20. His technique involves a retrocolic anastomosis with a restricted valvular opening between the gastric remnant and the jejunum.

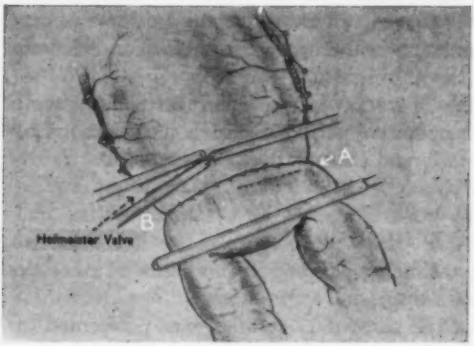

FIG. 1.—Valvular anastomosis.

Assuming that the previously stated causes are correct, it would appear that to obviate post-cibal symptoms, it is essential to adopt a technique which fulfils the following desiderata:—

(1) It must prevent a too rapid escape of gastric contents into the efferent loop and at the same time prevent any leak at all into the afferent loop. This may be obtained by fashioning a valvular type of anastomosis in which the width of the stoma should be two or three fingers in breadth, the afferent loop being attached to the lesser curvature (fig. 1).

(2) It must prevent the accumulation of bile and duodenal secretions in the afferent loop, while at the same time permitting of their easy egress. To effect this, the afferent loop must not be unduly long, nor must it lie in such a position as to be liable to kinking or to be subjected to undue tension when the final anastomosis has been completed. If a sufficiently high gastric resection has been effected, an antecolic valvular anastomosis will almost certainly angulate at the lesser curvature. If the afferent loop is to be short and incorporated in the valve by a suture to the stomach, and if the line of transection of the stomach is to be sufficiently high adequately to diminish a high acid secretion, we believe, as the result of our personal experience of sixty gastrectomies, that the anastomosis is best effected by a method

described some years ago by Lahey (1933) and Devine (1940), to which our attention has been drawn in a recent article by Ogilvie (1947). This involves the mobilization of the duodeno-jejunal flexure and its displacement upward into the lesser peritoneal cavity above the line of attachment of the transverse mesocolon. This enables one to effect a combination of a short retrocolic afferent loop attached to the stomach without tension or kinking. The anastomosis, on completion, is allowed to retract to the position of rest under cover of the ribs. The opening in the transverse mesocolon is loosely attached to the issuing efferent loop only.

The gratifying feature of this operation has been a remarkably smooth and uneventful immediate postoperative period in which the afferent loop and stomach remnant empty early and easily, with a low incidence of early or late post-cibal symptoms.

TECHNIQUE

With minor modifications the technique adopted in this series of cases has been uniform, its main features being:—

Incision.—In 90 per cent. of the cases the operation was performed for duodenal ulceration, and a right high paramedian incision was usual. In four cases in which the patients were obese, a transverse incision gave a more satisfactory exposure.

Duodenal closure.—If it is decided that the ulcer is resectable, the omentum is separated from the stomach, the blood supply of the former being preserved by ligation of the supplying vessels from the gastro-epiploic arch in close proximity to the greater curvature, one by one until the lower border of the pylorus is reached. The right gastric artery is ligatured, and the first part of the duodenum freely mobilized. A single Parker Kerr clamp is applied just distal to the pyloric ring, and the duodenum divided on the distal side of the clamp with a scalpel. The cut edge of the duodenum is caught in Poirier tissue forceps and the operative field kept free from escaping duodenal contents with a sucker. The stomach is pulled to the left, out of the operative field, and any necessary final dissection of the duodenal stump proceeded with. In dividing the adhesions on the posterior surface of the distal duodenum, the finest hæmostats are used and no forceps are applied to the duodenal side. No crushing instrument is applied to the duodenum at any juncture, in an effort not to jeopardize its already precarious vascular supply. If the ulcer is posterior and penetrating the pancreas, no attempt is made to remove it, but it is cut across.

The duodenum is now closed in three layers. The first consists of interrupted sutures of No. 60 thread, the suture line being inverted by a series of invaginating Lembert sero-muscular sutures. This in turn is buried by a further insertion of interrupted sutures in a usually thickened sheath of the pancreas to the anterior wall of the duodenum. In a few cases we found it an advantage to apply the stitches perpendicularly instead of horizontally —left to right—as is the usual procedure.

In three cases the ulcer was surrounded by an indurated inflammatory mass and was considered definitely non-resectable. In each case the Wangensteen modification of the Bancroft procedure was adopted, the postoperative period and subsequent progress being uncomplicated. In one case, in which there was a large penetrating posterior wall ulcer, a Nissen closure was adopted.

The anastomosis.—Attention is now again directed to the stomach, and the final clearing of the greater curvature is carried beyond the lowest of the vasa brevia. The left gastric artery is ligated separately, close to its origin from the cœliac axis. The lesser curve is freed of fatty tissue, and the portion to be involved in the anastomosis and above, is reperitonealized with a few interrupted sero-muscular sutures.

The duodeno-jejunal flexure is next identified, and with the mesocolon held taut by an assistant, it is completely freed of its attached peritoneal folds by scissors dissection, care being taken to avoid the inferior mesenteric vein as it lies in the anterior wall of the paraduodenal fossa. A hiatus is then fashioned in an adjacent avascular part of the mesocolon and the proximal jejunum delivered upwards, when it is found that the duodeno-jejunal flexure is now automatically transposed above the line of attachment to the mesocolon. The segment of jejunum to be utilized in the anastomosis is now selected and the anastomosis proceeded with. The sero-muscular suture unites the jejunum to the stomach throughout its entire length. The valve is fashioned in a manner indicated in figure 1, with the stomach *in situ*.

FIG. 2.—Gastro-duodenectomy completed.

Having excised not less than three-fourths of the stomach, in cases of duodenal ulcer the gastro-jejunal anastomosis is completed in the usual manner, the returning sero-muscular stitch securing the proximal jejunum over that portion of the stomach already closed. A few interrupted sero-muscular sutures are inserted along the suture line and at either extremity. The anastomosis is then allowed to fall back under the cover of the ribs leaving the whole of the short afferent loop in the lesser sac free from any tension or distortion. The hiatus in the mesocolon is affixed to the efferent loop only in the position which it takes up after the stomach remnant retracts upwards. In other words, the jejunum is brought up to the stomach and *not* the stomach to the jejunum (fig. 2).

The operation is completed by closure of the abdomen without drainage.

RESULTS

Immediate.—This series consists of 60 gastrectomies performed during the past two years, in which the described technique has been used. It includes only elective operations for peptic ulceration, 55 of the cases being of duodenal situation. There were two deaths: one from a pulmonary embolus in an ambulant convalescent patient on the fourteenth day, and the other from broncho-pneumonia on the sixth postoperative day. There was no incidence of intraperitoneal leak, hæmorrhage or wound infection.

In no case in this series did the immediate postoperative period give cause for anxiety. The afferent loop empties early, bile usually being present in the gastric aspirations on the first postoperative day. Intermittent gastric aspiration for the first two or three postoperative days only has been our routine, and has revealed a satisfactory emptying gastric remnant. In only two cases has the quantity of gastric residue indicated a temporary resort to continuous aspiration.

Late.—The period between the operation and its review varied from two months to two years. Two of the patients remain untraced and it was learned that they had emigrated, but were perfectly fit when they left the country. The remaining 56 patients have been examined many times through our Follow-up Clinic, and finally by postal questionnaire. Of these 56 cases, we have judged two only to have had definite sequelæ attributable to the operation. One describes the characteristic fullness and nausea after meals, but he does not experience drowsiness, sweating, or any other concomitant side-effects. The other patient complained of failure to gain weight, vague abdominal pains occurring irrespective of the ingestion of food, and sporadic diarrhœa. A barium meal revealed a 'spiky' appearance of the efferent jejunum similar to that of two cases reported by Stephen (1948-49) and ascribed to chronic jejunitis occurring in the efferent loop. His symptoms have gradually resolved spontaneously, and today, eighteen months following operation, he is well, gaining weight, and doing a full day's work. A further barium meal examination has not been performed. Of the remaining 54 cases, all but one are well and doing a full day's work without gastric disturbances. This patient replied to our questionnaire stating that he is on light work, but remains intolerant to fatty foods which evoke a feeling of fullness.

Our most cordial and appreciative thanks are due to our anæsthetist, Dr. Vernon Edwards of Felixstowe, and we also desire to express our thanks to Dr. J. R. B. McBride of East Bergholt, for the drawings.

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THE CORPSE IN HARLEY STREET

By LAURENCE DOPSON

On a Thursday morning in June 1880 the decomposed body of a woman was found in the cellars of No. 139 Harley Street. Although Harley Street was not at that time fully occupied by the medical and dental professions, it was nevertheless a very respectable street. Not before or since has anything else of the kind occurred there, and the only other time when Harley Street has been in the news for a criminal offence was in 1775, when Dr. Daniel Perreau, a fashionable Harley Street physician, and his brother, Robert Perreau, were hanged at Tyburn for forgery.

A murder mystery always has a fascination, and the story of the corpse at No. 139 Harley Street has even a certain nostalgic flavour, giving a glimpse of a life that has gone; a spacious age in which the 'below stairs' in Harley Street were inhabited by a hierarchy of butlers, footmen, menial servants, cooks and caretakers, instead of being consulting rooms; a time when foul smells were almost accepted as an inevitable accompaniment of drains; an era when the master and mistress went to the country for the summer months, accompanied by the servants to wait upon them. The more leisurely nature of that late Victorian age is epitomized at the outset by the fact that although the body was discovered on Thursday, the news was only published in *The Times* on Saturday.

DISCOVERY OF THE BODY

In 1880, No. 139 Harley Street was occupied by Mr. J. Q. Henriques, a respectable banker who had lived there for a quarter of a century. For a couple of years past there had been a rather bad smell in the cellars. Repairs were done to a cistern and the drains, and it was thought that this brought improvement; but it was soon found that the smell grew worse, and with the warmth of the summer in 1880 it became intolerable. It seemed to arise from one of the cellars where there was a large iron cistern. The footman who had to clean the boots in this cellar, at last could stand the stench no longer and drew the attention of his superior—the butler—to it. Underneath the cistern was a large barrel, of the kind used for delivering goods to the house. It was standing on its end, and the upper part was full of old bottles, gallipots, bits of rope, and so forth (fig. 1). With some difficulty (for it was very heavy) the barrel was dragged out. The butler, John Spenlove, started removing the rubbish which it contained and then suddenly cried: 'There's somebody in there!' The decomposed legs and one arm of a woman were visible.

The police were sent for and they removed the body to Marylebone Workhouse, where it was examined by Drs. Bond and Spurgin. Dr. Spurgin's report was shown to the Medico-Legal Society fifty years later by his son, Dr. Percy B. Spurgin, whose paper (*Transactions of the Medico-Legal Society*, 1931, **25**, 12) gives other interesting details of the crime. Dr.

Spurgin found that the body had been placed in the barrel with the head downwards and doubled backwards to the right. The right arm was flexed and doubled over the right breast, the hand being partly closed. The corpse was that of a woman aged forty to forty-five, 'although she may have been younger'. That she was 'a woman in the lower station of life' was indicated by the remains of her clothing, which showed it to be of a coarse nature. A common red glass bead was found embedded in the neck.

The face was unrecognizable, and the whole body was much decomposed and in part dried and mummified. Dr. Spurgin was of opinion that the woman had been dead for about two years. On the left breast was a wound between the 4th and 5th ribs, which he considered to have been the cause of death. The lung had completely disappeared and only the lower edges of the opening existed entire. When the front of the chest wall was removed it was found that the cartilages of the ribs had to be cut through, except

Fig. 1.—The cellar and the barrel containing the remains of the victim.

those above this opening on the left side, and of these the 2nd, 3rd and 4th ribs were found already separated from their cartilages, the 1st rib being entire. A knife found in the barrel could have caused the wound. Dr. Spurgin concluded that the body had been buried in, or covered with, chloride of lime before being placed in the cask, for only a very small quantity of the substance was found in the interior of the cask and none in the cracks; the body and remains of clothing were encrusted with it.

Through the courtesy of the Commissioner of Police of the Metropolis, I have seen the exhibits of this crime, which were presented to the 'Black Museum' at New Scotland Yard some years ago by Dr. Spurgin. They consist of some dark-brown, wavy, rather pretty hair; a portion of a stocking and garter with the lime still adhering (Dr. Spurgin's report in 1880 said that the legs of the body bore the remains of stockings 'and were gartered

above the knees with elastic garters having metal buckles'); portions of drawers and embroidery; and three casts of teeth, showing the teeth with the mouth closed, the upper jaw and the lower jaw. These casts of the teeth were the subject of controversy at the time. Mr. H. Braun, dental surgeon, of 384 Oxford Street, wrote the following letter which was published in *The Times* of June 16, 1880:—

'Being the dentist employed by Dr. Spurgin in this case to make casts of the mouth, &c., I consider it my bounden duty to contradict the general opinion as regards the teeth having been sawn or filed. On the contrary, the deceased would have been noted during life for having short, strong, and regular teeth, fitting edge to edge. I have also prepared a model of the mouth, showing as near as possible its appearance during life, and anyone wishing to view it can do so by appointment at the above address. As these points are important, I trust you will give this letter space in your columns. I was present at the inquest on behalf of the police, but was not called.'

EVIDENCE AT THE INQUEST

Inquiries were set afoot by Inspectors Lucas and King of the Divisional Police, assisted by Inspectors Greenham and Swanson of the Yard. The inquest was opened with formal medical evidence and was adjourned. When it was resumed on June 15 there was given what the newspaper described as evidence 'of a serious and significant character'.

Harry Smith, a young man in soldier's uniform, said he had been butler to Mr. Henriques three years ago, and had been sacked for being 'found the worse for drink'. 'I knew of a case of disorderly conduct on the part of a footman while I was there', said Smith, 'He used to stop out at night, and I had to let him in'. Then Smith went on to say that about August or the autumn of 1878 he had a man to dig in one of the cellars. 'I had a great accumulation of stale bread at the time, and I thought I should get into trouble, so I would have a hole to bury it'.

Other servants denied that there had ever been any quantity of stale bread in the house. Mrs. Jewry, who had been the cook from 1874 to 1879, said there had never been any waste bread 'and in the most emphatic terms denied that it would have been necessary for Smith to have had holes dug to bury it. Moreover, if there had been a waste, the dustman would gladly have taken it'. William Tinapp, a German footman, deposed that refuse of the kitchen was thrown in the dust-hole: 'I never saw any large quantity of waste bread in the house'.

John Green, the 'odd man', whom Smith had said he had had to dig the hole, declared: 'I did not dig any hole. I relaid the bricks. I did not ask Smith what he took them up for'. Green was taken to the house to identify where he had relaid the bricks. It was in a different cellar to the one in which the body was found, and when opened it was discovered that two stones had been let in to cover the place where a cesspool had formerly been (cesspool drainage in Harley Street!). No examination was made, apparently, to find traces of chloride of lime or of bread there.

Various servants gave evidence as to how long the barrel had been in the cellar. Knapp said that he went into Mr. Henriques' service in August

1878 when Smith was the butler, and he believed the barrel was in the cellar then. George Campbell, a servant, John Bootham, a butler, and George Minton, a footman, testified that there was no cask in 1877—and no smell. Mr. Woodroffee, caretaker of the house, said that in the autumn of 1878 he went into the cellar to hunt out a rat, 'and saw the barrel, for I knocked a stick against it'. Smith was the butler then, 'but was with the family in the country'.

THE VERDICT

On this evidence the jury brought in a verdict of murder by a person unknown. Theoretically, since the wound was on the left side of the breast, the fatal wound might have been self-inflicted, but, considering all things, this does not appear probable. It was not accepted as the explanation at the time, and the police offered £500 for evidence to convict the murderer.

Had the murderer used quick lime, instead of chloride of lime, his deed might never have been discovered. Such confusion of substances with similar names would be sufficient to plough the poor candidate taking 1st M.B. chemistry, but it was a mistake that was not enough to bring the murderer to justice. The knife and other implements found in the cask must have borne finger-prints of the murderer—but in 1880 there was no finger-print system; it was not until the next century that finger-prints were used to track the brothers Stratton who committed the Deptford murder in 1905. Finger-prints might also have established the identity of the body. As it is, the Harley Street case remains the mystery of the murder of a woman unknown by a person unknown. Perhaps the police knew who committed the crime, but could not produce the necessary evidence. So the murderer escaped.

CONCLUSION

But what of the other figures in the story? Mr. Henriques, whose quiet quarter-century of occupancy of the house in Harley Street had been disturbed so rudely, continued to live there until his death in 1898, and presumably had no trouble with the servants, despite the sinister associations. On October 17, 1898, a new name appears in the rate books of the vestry of St. Marylebone parish as occupier of No. 139—that of Alice Henriques. On January 15, 1899, the house is noted as 'empty'. Thereafter, old Mr. Henriques being dead and his family gone, the name of Henriques ceases to be associated with No. 139.

The Harley Street murder is forgotten. And so are the days when each house in Harley Street had its cook and butler and footman and under-servants—an age which has disappeared along with the straw which doctors used to lay on the roadway in front of their houses in Harley Street when they had a patient there who was dangerously ill.

I wish to thank the Commissioner of Police of the Metropolis and members of his staff at New Scotland Yard, and the Borough Librarian of St. Marylebone for their assistance. The illustration is reproduced from *Lloyd's Weekly News*, December 8, 1907.

CURRENT THERAPEUTICS

XXXIII—THE NEWER INSULINS

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A period of over twenty-five years has now elapsed since insulin with all its attendant benefits to the diabetic came into general clinical use. During that time continued search has been made to modify soluble insulin or evolve a new insulin combination which would provide better control of the blood sugar and avoid the drawbacks and difficulties met with in the use of insulin as time progressed. None of the insulin preparations so far has achieved ideal control of the more severe type of diabetes. None enables the physician to maintain the blood sugar within normal limits during the whole day's cycle and at the same time avoid hypoglycæmia. Soluble insulin requires at least two daily injections; its maximum effect in reducing the blood sugar occurs in three to four hours, and thereafter the blood sugar continues to increase. In the severe diabetic, indeed, during the overnight period the disease is relatively uncontrolled, and before the morning injection hyperglycæmia is at its maximum and temporary acidosis may have supervened.

MODIFIED INSULINS

The first of the modified insulins, 'insulin retard' of Hagedorn, was designed to act more slowly and to produce a more continuous effect. This early modification was followed by protaminé insulin, protamine-zinc insulin and more recently by globin insulin. The protamine combined types are slow acting. Their use is ideal for the mild diabetic in the later decades when the diabetic tendency cannot be controlled by diet alone; but their use in more severe types of diabetes is contraindicated, since they fail completely to control postprandial hyperglycæmia during the day, even when the dose may be sufficient to produce orthoglycæmia next morning or even symptomatic hypoglycæmia. Furthermore, when hypoglycæmia occurs the symptoms may be very severe and prolonged on account of the onset after a period of gradual fall in the blood sugar to very low levels. The effect of globin insulin is midway between that of soluble insulin and protamine zinc insulin. The maximum time of activity is some eight hours after the previous dose, usually between four to five o'clock in the afternoon. Unless the dosage is such as to reduce the blood sugar level too far at this time, postprandial and pre-breakfast hyperglycæmia may remain uncontrolled.

Although these two types of insulin have the common advantage of requiring a single daily injection only, both have other disadvantages. In the first place, neither enables the patient to combat the acidotic effects of an intercurrent infection so well as soluble insulin, and when acute illness ensues it is usually necessary to change to soluble insulin. Secondly, both are more commonly associated with local anaphylactic reactions than soluble insulin, and both are more liable to produce atrophy of subcutaneous tissues and fat depots at the sites of injection, the end-results of which may form a disfigurement, especially in the upper arm.

Various combinations of soluble with protamine or globin insulin have been tried by different workers, including soluble plus protamine insulin in one daily morning injection; soluble plus globin insulin in one injection; soluble plus protamine or globin in the morning with a dose of soluble at night; soluble in the morning with soluble plus globin at night, and so on. The physician must be very conversant with the timing of insulin effects to use these methods, but even then he cannot ensure that the effects will be constant, since an inconstant proportion of the soluble insulin may be retarded when mixed with the delayed insulin either in the syringe or before absorption from the tissues at the site of injection. This uncertainty may be more pronounced if a fibro-lipomatous tumour has been produced by too frequent injections over the same site.

The ideal insulin should be constant in its action, relatively rapid in its reaction to absorbed glucose, and sufficiently delayed and controlled in its later effects to maintain a normal level of the blood sugar without producing hypoglycæmia, and it should not produce any type of local reaction. Such an insulin has not yet been found, but in recent years attempts have been made to achieve this ideal with several newer types of insulin. Among these new forms are (a) modifications of the existing insulins, and (b) new types including iso-insulin, di-insulin, and polyvinyl insulin (subtosan insulin).

Modified protamine insulin (N.P.H. –50), which is neutral in reaction and contains 0.50 mg. crystalline protamine per 100 units, has been tried out on a large scale in Joslin's Clinic by Priscilla White (1949). In 336 patients, including 76 adults and 260 under twenty years of age, and all suffering from diabetes of moderate to severe degree, this type of insulin was found to begin to reduce the blood sugar in two hours, to produce its maximum effect in ten to twenty hours, and to influence the blood sugar for a duration of twenty-eight to thirty hours. Most patients required larger doses of N.P.H. –50 than of crystalline plus protamine types of insulin, but the author concluded that in 95 per cent. of the cases this form of insulin was used as successfully, if not more so, than separate injections of crystalline and protamine zinc insulins, and had the advantage of one daily injection only. It was a desirable form of insulin for the treatment of severe labile diabetes.

ISO-INSULIN AND DI-INSULIN

Iso-insulin is a form of retarded insulin but not in combination with a protein or a protamine. Modifications of the insulin molecule, which

contains the amino-acids histidine, arginine and lysine, may be obtained by titration of the amino groups. When brought in contact with reactive molecules like isocyanates, a stable linkage occurs with the amino groups. Iso-insulin was obtained in this way by Hallas-Møller (1944, 1945), the derivative being phenyl-ureido-insulin, in its chemical constitution. In its action on the blood sugar iso-insulin is retarded, but can be combined with soluble insulin. The mixture is permanent and is such that none of the soluble component is retarded by the iso type. It is thus possible to get a clear-cut immediate effect of the soluble insulin and thereafter a prolonged effect of the iso type. This combination, which goes under the name of 'di-insulin (Novo)', keeps well as a mixture in the same phial. This is an advance over the use of a combination of soluble insulin and any of the other retarded types, when the insulin requires to be mixed in the syringe at the time of injection or given in two separate injections.

During the past five years several workers have tried the effect of iso-insulin and di-insulin. Hallas-Møller and Hey (1944) compared the effect of iso-insulin with insulin retard and protamine zinc insulin. Iso-insulin was superior to both and in a single dose of 60 units maintained in diabetic patients blood sugar values of between 80 and 200 mg. per cent. for periods of at least sixteen to twenty hours daily. This was a big improvement as compared with one similar injection of crystalline insulin. Hey (1945) found that the blood sugar could be maintained within the limits of 120 to 200 mg. per cent. with 64 units of iso-insulin in two daily injections, a satisfactory degree of control which was not achieved by an equivalent amount of soluble insulin in four daily injections. With one injection of 40 units of di-insulin the blood sugar fell from 220 to 60 mg. per cent. within four hours, remained at 140 mg. per cent. for a further eight hours, and rose to the region of the fasting level thereafter. With two daily injections of 36 units of di-insulin, the blood sugar could be kept within the normal range without the occurrence of hypoglycæmia. It seems obvious from the charts that one daily dose of di-insulin sufficient to maintain the blood sugar below 180 mg. per cent. would produce hypoglycæmia some three to four hours after injection.

Brull *et al.* (1947) observed the blood sugar values for 36 hours in a male diabetic aged twenty-seven years with one daily injection of di-insulin. The blood-sugar fell in four hours from 200 mg. to 60 mg. per cent., and remained under 100 mg. per cent. for thirty-six hours. They treated 17 new cases of adult diabetes with di-insulin, with single daily injections in five cases and double daily injections in 12 cases, up to a maximal total of 100 units, reaching equilibrium and control in three to seventeen days with an average period of seven days. In 9 patients previously treated with soluble insulin or protamine zinc insulin or a combination of both, the total units used when changed to di-insulin fell by 50 per cent. In 42 patients treated with di-insulin, only 5 showed mild hypoglycæmia during stabilization. No local reactions were met with in this group.

These observers concluded that the effect of this type of insulin was superior to soluble insulin or protamine zinc insulin in reduction of the

total units required to maintain orthoglycæmia without the occurrence of biochemical hypoglycæmia, except on rare occasions, and felt that diabetics needing large doses of insulin were benefited by a change to di-insulin.

Boulin *et al.* (1947) changed eight diabetic patients treated with protamine zinc insulin to di-insulin in the same dosage while on similar diets containing 190 g. carbohydrate. The effect was better both in the level of the fasting blood sugar and in the excretion of urinary glucose. There were no local reactions, but hypoglycæmia was more frequent with di-insulin but not of severe degree. These authors considered di-insulin to be very effective, but concluded that dosage of over 30 units daily should be given in two injections to avoid hypoglycæmia.

Slessor and Nicol (1947) treated 12 diabetic patients with di-insulin and found that when dosage was under 50 units daily di-insulin could be used as a single daily injection, but that when requirements were above 50 units, the dose should be divided into two injections to avoid hypoglycæmia. After treatment for two to six months no local or general untoward reactions were experienced. Gerritzen (1948) found that di-insulin had an effect on the blood sugar midway between that of soluble insulin and protamine zinc insulin. Mlady (1948) used di-insulin in the treatment of 48 diabetic patients. The diurnal blood sugar curves seemed to be more regular with fewer injections and the tendency to hypoglycæmia was less pronounced.

Kesterman and Thöne (1949), from experience with 45 diabetic patients, found that iso-insulin exerted a protracted effect on the blood sugar and that di-insulin showed an immediate effect as well as a protracted effect in reduction of the blood sugar value. Thélin (1948), in the treatment of 7 patients with diabetes, found that a single dose of di-insulin gave better control than a single dose of soluble insulin, and that a single dose of 50 units of di-insulin was equivalent to two separate doses of 20 and 30 units of soluble insulin. Thélin concluded that di-insulin was a useful addition to the therapeutics of diabetes.

POLYVINYL INSULIN

In a further search for a retarding agent for insulin, Durel and Dubost (1945) aroused interest in polyvinyl-pyrrolidone for this purpose. This synthetic substance of high molecular weight is water-soluble and possesses physico-chemical properties akin to those of proteins. Using a combination of 25 per cent. polyvinyl-pyrrolidone ('subtosan') in soluble insulin in the treatment of diabetic patients, they found that it delayed the effects of insulin, with constancy.

Harvier and his co-workers (1947) compared the effect of this insulin with the protamine zinc type. In mild diabetes requiring only 10 units of insulin daily, the elimination of urinary glucose was similar with both types of insulin but the effect on the diurnal blood sugar curve was better with subtosan insulin. In more severe diabetes, 20 units of subtosan

insulin produced a lower blood sugar curve over ten hours than protamine insulin. The authors concluded from their data that the action of polyvinyl insulin was at least as good if not superior to protamine insulin, and that it had the advantage of being a homogeneous mixture. Choay and Choay (1947) came to a similar conclusion from investigations on 8 diabetic patients.

Subtosan insulin is the colour of pale clear serum, slightly viscous, and requires to be warmed before injection. An obvious objection to its use is that it requires a large needle (0.6 to 0.8 mm.) for injection. A supply of this insulin has been obtained, and preliminary results are encouraging.

In a male patient, aged thirty-nine, known to have had mild diabetes for four years, and whose symptoms became acute in March 1950, the diurnal blood sugar values were 246, 270, 200 and 272 mg. per cent. without insulin and the urine contained 192 g. glucose. Polyvinyl insulin was started in dosage of 20 units daily. After ten days on this dose the diurnal blood sugar values were 194, 150, 173, 250 mg. per cent. with 50 g. sugar in the urine.

In a female patient, aged fifty-six, with diabetic symptoms for nine weeks and septic feet for six weeks, the diurnal blood sugar values without insulin were 185, 201, 142, 285 mg. per cent. After twelve days on polyvinyl insulin, 16 units daily, the diurnal curve was 171, 148, 142, 217 mg. per cent. with 10 g. sugar in the urine. A comparative curve on 16 units protamine zinc insulin was 177, 142, 112, 138 mg. per cent. with no sugar in the urine.

In a female patient, aged fifty-six, the diurnal curve on 15 units soluble insulin twice daily was 200, 230, 190, 165 mg. per cent. with 22 g. sugar in the urine. On 30 units of polyvinyl insulin once daily, after three days the comparative figures were 176, 189, 100 and 198 with 17 g. glucose in the urine.

In two instances the effect of polyvinyl insulin was superior to that of protamine zinc insulin and soluble insulin in equivalent dosage. Further experience with this type of insulin is being acquired.

TRIAL OF DI-INSULIN

Preliminary trials have been made with di-insulin (Novo) under hospital observation. The general scheme of the experiments was to determine the degree of control on the previous type of insulin, if any, by recording: (a) the amount of sugar in the urine in each specimen passed and the presence of acetone; (b) the total amount of sugar in the twenty-four hours' collection of urine; (c) the diurnal curve of the blood sugar from blood samples taken at 8 a.m. (fasting), 11 a.m., 4 p.m. and 9.30 p.m.

The diets given were standardized to contain 2,108 calories with 170 g. carbohydrate, 86 g. protein, and 120 g. fat, the carbohydrate while on di-insulin to be given as one-third (57 g.) at breakfast, one-third (57 g.) at lunch, and one-third (57 g.) divided between tea and supper.

Case 1: Male, aged thirty-eight years. The patient developed diabetes in 1942, at the age of thirty, with symptoms of intense thirst and polyuria for six weeks before admission to hospital. The blood sugar was 462 mg. per cent. on Jan. 16, 1942. Treatment was started with soluble insulin, 25 units three times daily for two days, and then 20 units twice daily for one week. Thereafter he was stabilized on

protamine zinc insulin, 16 units daily. He remained well until 1948, when he injured his leg at work and an indolent ulcer remained at the site. Insulin was increased to 28 units (P.Z.I.), and the ulcer healed, but varicose veins of the leg were present and these were excised two months later. In March 1950, he was admitted to hospital with pneumonia. The insulin was changed to 25 units soluble twice daily. After discharge he developed a peripheral neuritis of the left arm with sensory defect in the left hand. The insulin dosage was 25 units twice daily. On this dose the blood sugar values were within normal limits—120, 112, 64, 62 mg. per cent. throughout the day—and the total excretion of sugar was negligible. Di-insulin was started in dosage of 36 units during this state of optimum control. After two days the diurnal curve was 219, 231, 239, 355 mg. per cent. The dosage was raised to 40 units, and after two further days the diurnal curve was 210, 163, 44, 182 mg. per cent., with 43 g. of glucose in the twenty-four hours' collection of

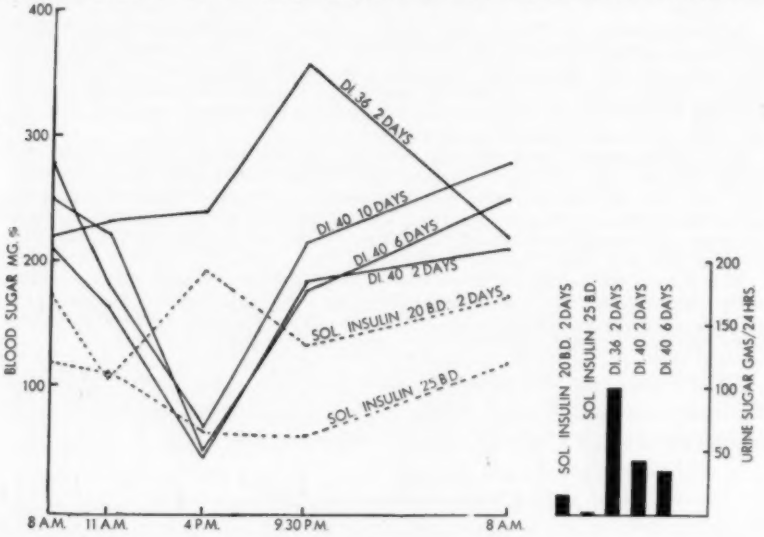

Fig. 1.—Case 1

urine, and four days later 250, 220, 50, 176 mg. per cent. with a daily loss of 34 g. urinary glucose. A further check after fourteen days on di-insulin showed 278, 181, 68, 214 mg. per cent. blood sugar (fig. 1). Thereafter the patient was placed on an equivalent number of units of soluble insulin, 20 units twice daily. After ten days the diurnal curve showed 173, 108, 191, 134 mg. per cent. of the blood sugar, and the total sugar excreted for the day was 15 g.

Case 2: Male, aged forty-five years. Diabetic symptoms had been present for eighteen months. He consulted his doctor nine months previously and was given a daily injection of insulin. Two months previously he ceased to attend for injections, and his symptoms of thirst, a sweet taste in the mouth, polyuria and weakness recurred. On admission to hospital he was a healthy-looking man, weight 146 lb. General clinical examination was entirely negative. His urine contained sugar but no acetone or albumin. A sugar tolerance test showed the following curve of moderate diabetes: fasting blood sugar, 261, 286, 296, 261, 227 mg. per cent. at further intervals of thirty minutes. He was given 20 units of di-insulin daily. After three days the diurnal blood sugar values were 216, 253, 264, 286 mg. per cent., and the urine contained 112 g. glucose. The insulin was then raised to 30 units. After three days

the diurnal curve was 229, 219, 66, 185 mg. per cent. and the urinary loss of glucose was 59 g. After a further period of three days the diurnal curve was 225, 214, 100, 221 mg. per cent., showing a constant degree of control. The urine at this time contained 81 g. glucose. The insulin was then increased to 36 units. After six days the diurnal blood sugar values were 227, 185, 50, 223 mg. per cent. and the urine contained 49 g. glucose. The patient was then put on two doses of soluble insulin, each of 16 units, and after two days the diurnal curve was 198, 154, 218, 150 mg. per cent., whilst the urine on this regime contained 22 g. glucose (fig. 2).

Case 3: Female, aged seventeen years. This girl was a moderately severe diabetic. Symptoms began at the age of fourteen, and over the intervening period the dosage required for control was two daily injections of 38 units soluble insulin. During this time she grew normally and put on weight from 130 to 154 lb., and menstruation was regular. The only complication was acute appendicitis in 1949. The patient made an uneventful recovery and continued thereafter on the same dose of insulin. Early in May 1950, she began to have repeated mild hypoglycæmic attacks and the insulin dosage was reduced to 32 plus 32 units. This was reduced to 25 plus 25 units on admission to hospital. After six days on this dosage the diurnal blood sugar values were 278, 318, 176 mg. per cent., and the urine contained 52 g. glucose. Di-insulin

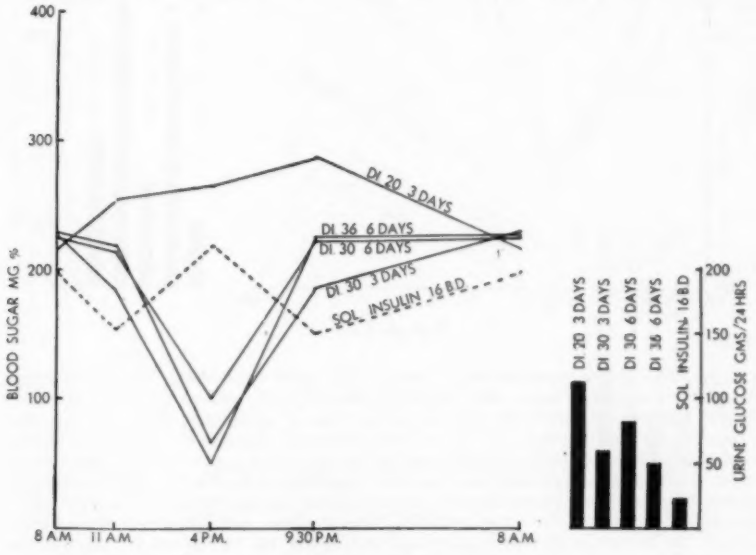

Fig. 2.—Case 2

was started in dosage of 40 units once daily. A hypoglycæmic attack occurred on the first day at 4 p.m. and required the administration of glucose. After three days on 40 units the diurnal blood sugar values were 334, 337, 177, 430 mg. per cent., and a similar curve was found two days later. On these two days the urine contained 211 and 87 g. glucose respectively. After eight days the diurnal curve was still 392, 280, 196, 490, mg. per cent. The insulin was raised to 50 units and after three days the diurnal values were 404, 362, 297, 266 mg. per cent. A further curve was found to be 393, 345, 194, 355 mg. per cent., after two days on one injection of 80 units of di-insulin, and the urine contained 118 g. glucose. During this time the patient experienced general malaise and headache; there was no pyrexia (fig. 3).

Case 4: Male, aged twenty-three years. This man was admitted to hospital in December 1949 with a history for six months of thirst, polyuria, cramps in the legs and loss of weight from 168 lb. to 140 lb. His occupation was a blacksmith. General clinical examination revealed no abnormality. Radiological examination of the chest showed normal lung fields. The urine contained sugar, a trace of acetone but no albumin. A sugar tolerance test gave a curve of moderate diabetes, a fasting blood sugar 191 mg. per cent., and values thirty minutes thereafter of 216, 281, 252, 236

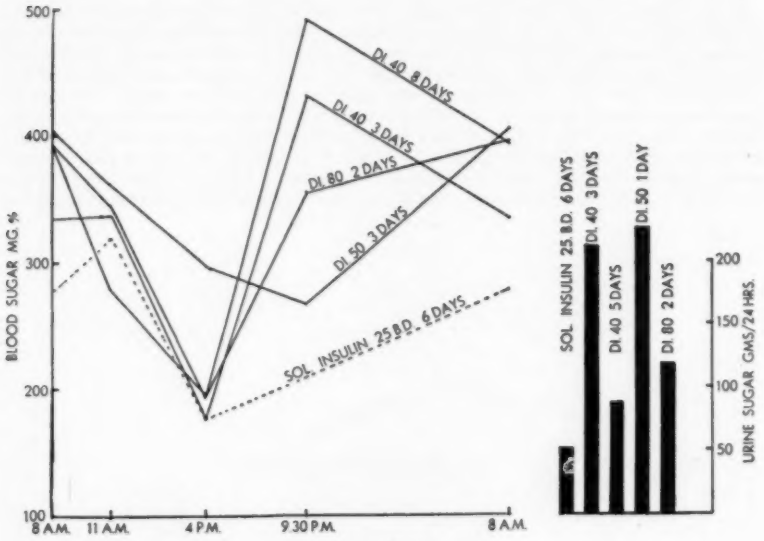

Fig. 3.—Case 3

mg. per cent. Insulin was started in dosage of 20 units twice daily. Within four days the urine was free of sugar and the fasting blood sugar was 90 mg. per cent. The insulin was reduced over the next seven days to 10 units twice daily. He was discharged on a diet of 3000 calories and with traces of sugar in the urine, the fasting blood sugar being 117 mg. per cent. and at 11 a.m. 129 mg. per cent. He returned to heavy work and experienced several mild hypoglycæmic attacks. His insulin was changed to 12 units protamine zinc, and thereafter he experienced no further hypoglycæmic symptoms, the urine remained free of sugar, and his weight increased to 161 lb. In May 1950 he was re-admitted to hospital. He had been off work for four days with a cold, and sugar was again found in the urine. On the first day with 12 units protamine zinc insulin the diurnal curve was 175, 299, 237, 428 mg. per cent. Di-insulin, 20 units daily, was started three days later. On the first day the diurnal curve was 144, 241, 104, 225 mg. per cent., and the urine showed a total of 35 g. glucose. After four days on this dose of di-insulin the diurnal curve was 170, 216, 273, 341 mg. per cent., and the urine contained 110 g. glucose. After six days the diurnal values were 163, 231, 126, 305 mg. per cent., and the urine showed 65 g. glucose. On 30 units di-insulin, the diurnal curve was 163, 90, 92, 252 mg. per cent., and the urine showed 44 g. glucose. Over nearly all this period the patient complained of malaise, headache and lack of strength and at this point the insulin was changed to 20 units protamine zinc type. The diurnal curve after nine days was 198, 222, 138, 357 mg. per cent., and the daily excretion of urinary glucose was 45 g. (fig. 4).

DISCUSSION

In our experience of this type of insulin the greatest effect on the blood sugar during the day was consistently in all cases at 4 p.m., that is, eight hours after injection. In patient No. 1 the blood sugar was completely controlled without symptomatic hypoglycæmia on 25 plus 25 units soluble insulin. With 20 units soluble insulin twice daily the diurnal curve was 173, 108, 191, 134 mg. per cent., with a loss of 15 g. urinary glucose, as compared with a diurnal curve of 278, 181, 68, 214 mg. per cent., with 34 g. sugar in the urine on 40 units di-insulin. The dose of di-insulin could not be raised above this level without producing hypoglycæmia at 4 p.m. It is possible that giving more carbohydrate at lunch or tea and less at breakfast might bring more uniformity in the diurnal curve. In case No. 2, 30 units

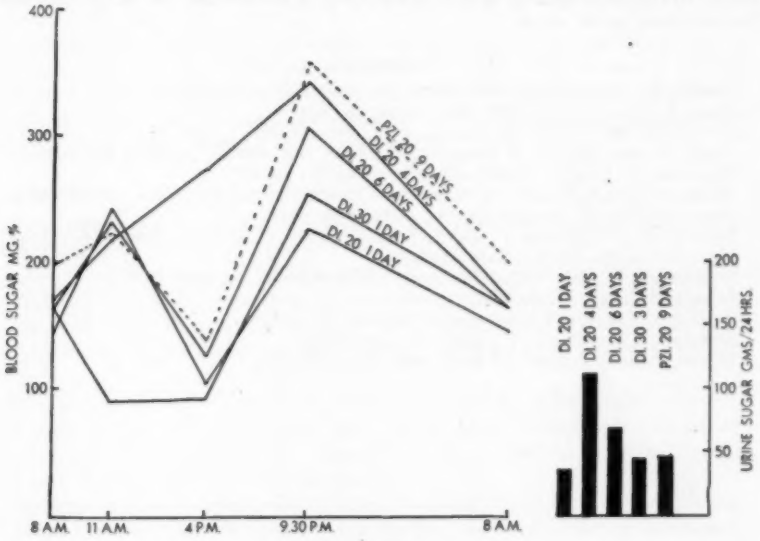

Fig. 4.—Case 4

of di-insulin maintained a constant degree of control over a space of five days, and on 36 units the diurnal curve showed 227, 185, 50, 223 mg. per cent., with a loss of 49 g. glucose, as compared with 198, 154, 218, 150 mg. per cent. and a loss of 22 g. glucose on two daily injections of 16 units soluble insulin. The effect of 32 units soluble insulin is rather better than that of 36 units of di-insulin. In patient No. 3 who had been previously well-controlled for two years on two daily injections of 38 units soluble insulin, two daily injections of 25 units soluble insulin gave a diurnal curve of 278, 318, 176 mg. per cent., with 52 g. of glucose in the urine, as compared with 404, 362, 297, 266 on 50 units di-insulin, and 80 units di-insulin

did not bring about orthoglycæmia. In patient No. 4 optimal control was not achieved with di-insulin, although the diurnal blood sugar curve was better on di-insulin, 30 units, than with protamine zinc insulin, 20 units.

It would require further experience of these types of insulin before any final opinion can be given about them, but the impression to date is that, in the absence of evidence of convincing superiority over the present types in use in this country, it would be inadvisable to advocate their use on any wide scale. It is true that in milder types of diabetes one daily injection of, say, up to 30 units of di-insulin gives effective control. With larger doses hypoglycæmia about 4 p.m. is likely to occur, and if two doses are used it is almost always as well to use soluble insulin.

We are indebted to the patients who submitted themselves over periods of several weeks for this investigation, and to Sister M. E. Thomson and Dr. A. M. Mackay for assistance in the wards.

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REVISION CORNER

VOMITING IN PREGNANCY

NAUSEA and vomiting are frequently experienced by women when pregnant. When therefore these are found in association with amenorrhœa it is often concluded that the subject affected is pregnant and that the vomiting is due to the pregnancy. Yet not all women who vomit and have amenorrhœa are pregnant, nor is vomiting during pregnancy always due to the pregnancy. It may be due to a variety of associated conditions, such as peptic ulcer, appendicitis, pyelitis, intestinal obstruction, cerebral disease, and the like. Moreover, the diagnosis of pregnancy itself is not always easy. Therefore when a woman in the child-bearing period of life complains of vomiting the practitioner must consider whether she is pregnant and, if so, whether the vomiting is due to the pregnancy or to some associated disorder.

Provided the possibility of associated vomiting is kept in mind, mistakes in diagnosis are less likely to be made, even if the responsible disease is rare or obscure. In some very acute cases of pyelitis, vomiting may be the predominating symptom. Personal experience of two cases of intestinal obstruction in pregnancy prompts me to draw attention to this possibility.

ETIOLOGY

As the etiology of the condition is not clearly understood the theories related to it are numerous.

Neurosis.—Some consider the vomiting to be the expression of a psychological conflict, a desire of the subconscious mind to be rid of the pregnancy. Not all women who vomit early in pregnancy are neurotic: yet there is often evidence of a psychological conflict and the effective result of suggestive treatment is well known.

Toxæmia theory.—In view of the widespread changes found at necropsy in fatal cases, the idea of a blood-borne toxin issuing from the developing ovum, or resulting from the breaking down of maternal tissues involved in the embedding of the ovum, is attractive but unsubstantiated.

Deficiency of liver glycogen resulting from the demands for carbohydrate by the growing fœtus has been postulated but is hard to credit, considering how small the fœtus is when the vomiting first begins.

Endocrine theories likewise have been suggested. Deficiency of corpus luteum, excess of corpus luteum, excess of gonadotrophic hormone, swelling of the anterior lobe of the pituitary gland causing cerebral vomiting, and cortico-adrenal insufficiency, have all been postulated but none substantiated.

Pathological changes.—In fatal cases the heart is found to be small, its muscle wall atrophied, and subendocardial hæmorrhages may be present. Capillary hæmorrhages are found in the hypothalamus of the brain, and the liver shows marked fatty infiltration. The changes in the brain may be due to vitamin B_1 deficiency, whilst the changes in the liver are those of starvation.

Whatever the cause of vomiting, if it is allowed to continue for long, depletion of the glycogen stores in the liver occurs. This leads to fatty degeneration from which recovery is possible if glucose in sufficient amount can be brought to the

liver before the degeneration has gone too far. In the latter event irreversible changes take place in the liver, and the waste products of metabolism cannot be detoxicated by it. Imperfect oxidation of fats leads to acidosis, and acidosis to further vomiting, which in a vicious circle leads to further liver damage.

CLINICAL CONSIDERATIONS

Morning sickness.—On rising in the morning the patient feels sick and vomits a small amount of clear or bile-stained mucus, but the preliminary retching may have been severe. She may then feel well and eat normally for the rest of the day. This sickness begins about six weeks after conception and lasts for about two months. It does not usually cause any constitutional disturbance, but in a few cases the vomiting becomes persistent and renders her incapable of leading her normal life: the condition is then known as hyperemesis gravidarum.

Hyperemesis gravidarum varies in gravity:—

(a) Mild and moderately severe cases. In these morning sickness gives place gradually to more frequent and more severe vomiting occurring at any time of the day, and usually precipitated by the taking of food. Retching and vomiting of small amounts of gastric secretion may occur in the intervals. Later, loss of weight, lassitude and weakness develop, the pulse rate rises to 90 or 100, and the blood pressure falls. The urine becomes scanty and highly coloured, contains ketone bodies, and the ammonia coefficient is raised.

(b) Severe cases are fortunately rare. The transition from morning sickness may be gradual, perhaps finally with deceptive suddenness, or the illness may be fulminating from the start. The vomiting is persistent, even fluids being rejected. The tongue becomes dry and furred or even red, the stomach dilated, the vomit coffee-ground, the pulse rate rises to 120 or 130, the blood pressure falls, pyrexia occurs, and jaundice may appear. The urine contains albumin, perhaps bile, ketone bodies are present, and the ammonia coefficient may rise to 20 or 30. Nystagmus and oculo-motor paralyses, moroseness, irritability, and confabulatory amnesia are of grave import, whilst lethargy, stupor and coma are terminal.

TREATMENT

Morning sickness.—In many cases no treatment is required. In others the taking of frequent small dry meals of high carbohydrate content, extra sugar or glucose, the drinking of adequate fluid between meals, and avoidance of fats may result in considerable improvement. The ritual of munching a dry biscuit before raising the head from the pillow in the morning may help the suggestible patient. The expectation of improvement should be encouraged.

Hyperemesis gravidarum.—The next step is removal of the patient to hospital where ordinary diet is given and facilities for vomiting are not provided. Many never vomit after entering hospital, yet they should not be discharged too promptly, for return to home and relatives may be followed by a recurrence. If vomiting continues, kindly yet firm handling is necessary. Visitors should be forbidden, and the quiet insistence that the patient should clean up the vomit from floor or bed clothes may have a salutary effect.

These measures failing, all oral ingestion should be forbidden and the continuous intravenous administration of 5 or 10 per cent. glucose in normal saline

(six pints in twenty-four hours) instituted. The saline content should be reduced as the vomiting becomes less. Aneurine (vitamin B_1), 10 mg. daily by intramuscular injection, may prevent neurological complications. Sleep should be secured by a parenteral sedative, e.g. paraldehyde, 10 ml. intramuscularly. After twenty-four hours without vomiting small quantities of barley sugar may be ingested, and after another forty-eight hours intravenous therapy is abandoned and fluid and carbohydrate given by mouth. Thereafter normal diet is gradually resumed. In the event of a recurrence the whole process must be begun again.

In these serious cases a watch must be kept for the danger signs, as termination of the pregnancy may become an urgent necessity. Marked loss of weight, pyrexia, pulse rate of 120 or more, fall of blood pressure, dry red tongue, jaundice, and blood in the vomit are grave signs. Their appearance in the course of treatment calls for termination of the pregnancy, usually by hysterotomy. The state in which ocular palsies, delirium and coma occur should never be allowed to develop, for recovery would then be highly improbable and termination of the pregnancy at that stage would be of no avail.

VOMITING IN LATE PREGNANCY

Vomiting in late pregnancy may be encountered in severe forms of pre-eclamptic toxæmia and in acute yellow atrophy. In these grave cases termination of the pregnancy is urgently required, and immediate hospital admission is imperative.

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TRACHEITIS

TRACHEITIS is a condition with which all medical men are familiar and which many believe they have themselves experienced. Yet there is little real evidence that the set of symptoms associated with tracheitis is in fact accompanied by a true inflammation of the trachea, since fatalities are rare and direct examinations of the mucous surface during the active phases of the inflammation are unusual. Tracheitis may occur in acute and chronic forms. It is an important, perhaps the initial, lesion in whooping-cough; it is always of consequence and sometimes fatal when it occurs in diphtheria, and it is much stressed at the present time as a manifestation of tuberculosis. Occurring in a group of its own is that type of tracheitis encountered in fulminating influenza and related to a virus. In viral tracheitis and tracheitis from other causes all grades of disturbance may be met with, down to inflammation of quite minor severity and extent. The use of the word tracheitis implies that although the trachea may not be the only site of inflammation it is the most important one. Tracheitis is a cause of real respiratory disability but of itself it produces no distinctive clinical or radiographical signs.

TYPES AND SYMPTOMS

Tuberculous tracheitis and *tracheo-bronchitis* are certainly as old as tuberculosis but the full implications of the localization and its impact on various therapeutic procedures have been realized only recently, so that the age-long occurrence of it has

been rather overlooked. It must certainly be taken account of and the possibility of its existence be considered in all cases because of its dire effect in collapse treatment, when it may lead to complete absorption collapse in part, or the whole, of a lung, and because of its dominating influence over pulmonary resection. In the influenzal variety there is severe injection of the mucous membrane with large areas of slough (if the patient survives long enough for these to form).

Apart from whooping-cough, *acute tracheitis* is rare in children, and as it ordinarily occurs affects middle-aged and elderly people. The boundary between tracheitis and large-tube bronchitis is not precise, but on the whole tracheitis is not associated with spasm, and a sensation of substernal rawness or even pain is frequent. The cough is irritable and nearly always painful; at first it is seldom productive. The temperature and pulse rate may be raised, but generally the constitutional features are not marked (save in the fulminating influenzal type). A cold, raw, foggy atmosphere is a frequent precipitating cause of acute tracheitis. Climatic conditions of this sort are probably of more importance than bacterial invasion, which is secondary, generally in the form of a mixed flora. Even in those cases which are climatically determined there is some evidence of a primary rôle being played by a virus.

The *chronic form* may follow on from an acute attack, or it may develop insidiously without any formal acute attack being experienced. Acute exacerbations are common; in fact they are the rule, and there is certainly a constitutional and perhaps a familial predisposition in some individuals. One attack predisposes to further attacks, especially when experienced early in the winter, in which event repetitions are frequent until the advent of warmer weather brings some respite and allows the irritability of the mucous membranes to become subdued. Factors which aggravate the tendency to chronicity are an unhealthy upper respiratory tract, particularly with the existence of chronic sinusitis, post-nasal catarrh, inflammatory hypertrophy of the tonsils or accessory lymphoid tissue in the pharynx, and smoking. The latter is an important source of irritation, and a smoky atmosphere is often as provocative to an individual as if he himself were smoking.

TREATMENT

An even and comfortably warm atmosphere is desirable in the management of these patients and in acute cases they should be confined to one room for the first forty-eight hours. There is some increase in mucus production, which is viscid, and until it becomes dislodged there is little virtue in coughing. In the early phases the act of coughing increases the irritation and discomfort, and prolonged spasms may be very exhausting. The most useful remedies are steam inhalations, sedative linctuses and lozenges. For the inhalation, the good old-fashioned Friar's balsam, to which one crystal of menthol is added, poured on to a pint of steaming water in a jug or earthenware inhaler, has few equals.

The sedative linctus is useful at night time:—

Solution of morphine acetate	8 minims (0.5 ml.)
Spirit of chloroform	3 minims (0.2 ml.)
Lemon juice	15 minims (1.0 ml.)
Mucilage of acacia	to 60 minims (3.5 ml.)

It should be sucked very slowly from a teaspoon and can be repeated once. The 'Brompton lozenge' maintains its reputation in these cases and is demulcent and

soothing. In the recovery stage, or as a preventative on raw winter days, a generous teaspoonful of cod-liver oil and malt thrice daily is recommended.

The more serious forms of tracheitis, particularly the fulminating influenzal type, clearly call for special consideration. Little benefit normally accrues from penicillin in ordinary doses, and sulphonamides are without effect. The value of the newer antibiotics has yet to be assessed, but in the existing state of knowledge *aureomycin* should certainly be given a trial. The suggested dose is 0.25 g. orally, every six hours to a total of 10 or 12 grammes. *Streptomycin*, in combination with *p-aminosalicylic acid* (P.A.S.), is indicated in the tuberculous type, and healing may be expected in many cases. If, however, the inflammation has gone deeply the healing will be at the expense of contraction and distortion of the lumen, and in some instances stenosis is the inevitable consequence.

KENNETH ROBSON, M.D., F.R.C.P.
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NOTES AND QUERIES

Spina Bifida and Heredity

QUERY.—I shall be glad if you can advise me on the following: A married couple have had a stillbirth of eight-and-a-half months, apparently normal at autopsy, followed by a live birth, a boy with talipes equinus. The family history is: Father's side, normal; Mother's side: mother (eldest child) normal; one brother had spina bifida and lived only a few months; one sister with spina bifida alive but lethargic and backward; one sister with spina bifida lived only a few months. If this couple have more children what are the chances of their (1) having spina bifida or other deformities; (2) being 'mongols' or mentally deficient? Are these chances greater than the average?

REPLY.—A geneticist would consider that three cases of spina bifida in one family indicated a strong dominant defect likely to be reproduced in collaterals. This view might be strengthened by the consideration of the married couple's family—one stillbirth, one congenital talipes. But, on the other hand, the three cases of spina bifida in one family are so unusual, so beyond one's clinical experience, that some factor, possibly environmental, other than hereditary, may be sought for, and it would not necessarily follow that the healthy member of that family had inherited that particular gene. In support of this, the family history of the married couple need not be considered so ominous. A stillbirth may be merely a misfortune, not of pathological significance; and congenital talipes may be due to abnormal pressure *in utero* without any heredity connexion. He would be a bold man who would promise that any subsequent addition to the family would not present some abnormality, but if the couple, with natural instinct, fervently desire a healthy child the risk would be worth taking.

SIR LANCELOT BARRINGTON-WARD, K.C.V.O., CH.M., F.R.C.S.

'Mucous Colitis'

QUERY.—I would be grateful for any information you could provide in treating an elderly lady who complains of mucous colitis, with its obvious inconvenience, accompanied by achlorhydria. Her trouble is worse in the morning, coming on during or after breakfast, and at times there is involuntary incontinence.

REPLY.—Mucous colitis is generally considered to be a colon neurosis, and time taken in reassuring the patient and distracting her attention from her stools is usually well spent. A simple ordinary diet with little residue is desirable, and processed brand and isogel or carbomucil are useful in ensuring soft bulky stools. Paroxysmal attacks of colic may be prevented by antispasmodics; for instance, a pill containing dry extract of belladonna, ¼ grain (16 mg.), and codeine, ½ grain (32 mg.), taken each morning. Alternatives are 'bellergal' or 'placadol', a new preparation containing papaverine hydrochloride and homatropine methylbromide. The diagnosis of mucous colitis is not often made nowadays. Organic disease must first be excluded by radiological and sigmoidoscopic examinations, for the passage of mucus may be a feature of carcinoma of the rectum or colon, polyposis, diverticulitis, and regional colitis. The presence of achlorhydria in the case in question calls for a blood examination to exclude pernicious anæmia, in which gastro-intestinal symptoms are not uncommon. In mucous colitis, constipation is the rule, and the fact that incontinence of fæces is noted during or after breakfast suggests that there may be intestinal irritation by undigested

food from the stomach, in which case treatment with glycerin of pepsin, 60 minims (3.5 ml.), and dilute hydrochloric acid, 30 minims (1.8 ml.), in a tumblerful of orange or lemon drink, sipped throughout each meal, may be effective.

W. H. HARGREAVES, O.B.E., F.R.C.P.
LIEUT.-COL. R.A.M.C.

Persistent Postoperative Penile Pain

QUERY.—My age is thirty-five years. Eight months ago I had a left ureteric stone removed from the lower end (about 1 inch above the intra-mural part) of the ureter. A urinary fistula developed through the abdominal incision, in spite of an attempt by the surgeon to obtain a dry suture line. I later developed a pyelonephritis which responded well to penicillin and sulphamezathine, and the urinary fistula then closed spontaneously. A check cystoscopy was carried out, and five days following I developed a constant desire to micturate, with penile pain, and this has persisted now for practically eight months, occasionally being a little better but never leaving me. I can sleep all right without any disturbance. Recent intravenous pyelography (I.V.P.) shows function in the concerned kidney although the lower end does not outline too well; there is no evidence of any hold-up. The urine is bacteriologically sterile and there are no other abnormalities.

I have been advised that I now have a spastic bladder and nothing can be done for it. I am managing with great difficulty to continue my practice duties as I am able to endure the pain and desire sufficiently not to need to micturate more than three- to four-hourly. I would be grateful for any advice that you could give me.

REPLY.—A lesion of the lower end of the ureter will often give rise to penile pain and increased frequency of micturition. It is not stated whether the ureter was catheterized at the time of the last cystoscopy, but the possibility is that there is some narrowing of the lower end at the site of the operation, and it would seem wise that the ureter should be catheterized and, if necessary, dilated at intervals. If this is not done there is a distinct possibility of further stone formation. Although the recent I.V.P. is said to show function in the kidney it is not stated whether there is any dilatation there. If there is no nocturnal disturbance and no more frequency than three- to four-hourly by day it would not appear that there is much spasm in the bladder. In the absence of any residual lesion in the lower end of the ureter, and in the presence of a sterile urine, it is pretty certain that the symptoms will gradually disappear; in the meantime small doses of veganin are most likely to relieve matters.

E. W. RICHES, M.S., F.R.C.S.

Intractable Acneiform Eruption

QUERY.—A schoolgirl, aged fifteen, suffers from an intractable skin disorder of acneiform type, affecting principally the forehead and face. The lesions are small red papules which cover the forehead in large numbers, the majority being associated with 'blackheads', and many becoming secondarily infected. The patient also suffers from migraine, and there is a family history of allergic and similar phenomena (urticaria, migraine, asthma). What part might hypersensitive phenomena play in the etiology of the skin condition? What effective methods of treatment exist?

REPLY.—The answer to this inquiry really depends upon the diagnosis. If the child is suffering from true acne vulgaris, then, for all practical purposes, hypersensitive factors play little part in the etiology of the skin condition. If the condition is due to exposure to oils to which she is exposed during some kind of work at school, then there may be a factor of sensitization, although this would seem to be unlikely. The condition might, however, be one of the rarer forms of tuberculous manifestation, in which the skin is possibly hypersensitive to tubercle bacilli or to some toxin derived from a tuberculous focus. The fact that blackheads are present, associated with the presumption that it is unlikely that she is exposed to oils that would produce acne, indicates that the diagnosis is probably acne vulgaris, in which case the application of the following paste at night should help, especially if she is encouraged to wash the area with soap and water before applying the paste in the evening, and again in the morning:—

Resorcin	6 per cent.
Precipitated sulphur	6 per cent.
Zinc oxide	12 per cent.
Lanolin.....	12 per cent.
Soft paraffin.....	to 1 ounce (28.5 g.)

If this fails, sterner measures, such as X-ray therapy, should be considered.

R. M. B. MACKENNA, M.D., F.R.C.P.

Chicken Mite Infestation

QUERY.—I wonder if you could help me to solve the answer to a problem, or rather to confirm it, since I think I have by something of a coincidence found the answer in the columns of your June issue? The enclosed slide is of an unknown (to me) parasite and the story attached to it is briefly as follows:—

Two American families are occupying one house in this area while the husbands are occupied in flying duties over here. I was rung up one morning by one of the wives who said that she had woken up to find a lot of 'bugs' on her pillow and in her hair. Thirty-six hours previously she had returned from a short visit to London and was afraid that she might have picked them up either at the hairdresser or on the railway. No other member of that small community appeared to be infested except her husband, and he only to a small degree.

I felt obliged to do my best to exonerate all parties concerned, and enlisted their cooperation to obtain some specimens. This they did, and I mounted a few for examination. I could not identify the creature, but at least felt I could confidently reassure them that it was no form of louse, as there were four pairs of legs. I thought it might be some type of harvest bug. I prescribed D.D.T. Application (N.F.) for the scalp and a similar spray for the bedroom. The effect was gradual but we won in the end. I have not yet confirmed complete victory, but will be doing so, I hope. Fortunately the parties concerned have a sense of humour and there has been no crisis! Then tonight, looking through the June issue of *The Practitioner* I found on page 567 a paragraph headed 'Chicken Mite Infestation', the illustration to which exactly, as I think, portrayed the unknown invader. An interesting point is, that none of those concerned has had anything to do with poultry of any kind, nor are there any poultry runs in the garden of the house, although there probably may be in neighbouring gardens. The house has fairly prominent eaves, and I understand that a large number of starlings nested thereunder, and the window of the bedroom in which the mites appeared is close to these nests. I wonder if these, or other birds, could possibly have been the primary hosts?

REPLY.—The chicken mite or red poultry mite, *Dermanyssus gallinæ*, is sometimes a troublesome pest of hens and may also invade houses and bite man. The mites may be carried into the house on the clothing of people tending the chickens, or they may be carried by other birds to nests in the eaves, whence they may gain access to bedrooms. The mite normally lives in the crevices of the chicken house, emerges at night to suck the birds' blood, and returns to its hiding place before dawn. The eggs are laid in the crevices and the whole life cycle takes only about two weeks.

To eradicate mites from an infested chicken house, all straw and litter should be removed and burnt. Then the interior is thoroughly sprayed with a preparation of *gamma* B.H.C. ('gammexane') or D.D.T. or possibly with a tar oil 'winter wash' insecticide. A similar treatment could be used for infested bird nests in the eaves, if that is the source of the mites. The attacks on humans (which can be very irritating) will not persist, if the source of infestation is cleared up.

J. R. BUSVINE, D.SC.

PRACTICAL NOTES

Procaine Penicillin in Pneumonia in Children

THE results obtained from the use of procaine penicillin in lobar and bronchial pneumonia in 91 children, aged 1 month to 12½ years, are recorded by J. F. Crigler *et al.* (*Journal of the American Medical Association*, June 10, 1950, **143**, 532). The preparation used was one containing crystalline penicillin G procaine suspended in peanut oil containing 2 per cent. aluminium monostearate, each ml. containing 300,000 units. The dosage schedule was :—

Weight of patient	Units of penicillin
Up to 10 lb.	300,000
10 to 15 lb.	450,000
15 to 20 lb.	600,000
20 to 30 lb.	900,000
30 lb. and over	1,200,000

Each child received one injection. The results were considered 'good' in 87 (96 per cent.), 64 of these children being afebrile within twenty-four hours of the injection of penicillin. Of the four failures, two recovered uneventfully after a second injection of penicillin. No allergic or local reactions to the procaine penicillin were observed. Serum penicillin levels were assayed on 475 occasions, and 'without exception, following any of the dosages used, the serum penicillin level was greater than 0.14 unit per cubic centimeter for four days after injection'. An interesting observation was that of the 52 estimations made within one hour of injection of the penicillin, the average serum level was over 2 units per ml., ranging from 0.6 to just over 3.0 units per ml. 'It is concluded that with the dosage schedule outlined, the single injection treatment with a repository penicillin of pneumonia in children is at least as effective as any other schedule of therapy. In outpatient clinic practice, consideration of economy and convenience make this the treatment of choice'.

Adult Enuresis and Hypersomnia

THE results of the study of 35 cases of adult enuresis (22 male and 13 female) are recorded by R. Ström-Olsen (*Lancet*, July 22, 1950, **ii**, 133). The ages of the patients ranged from sixteen to forty-one years. Of the 35 patients the question of hypersomnia was not investigated in 7; of the remaining 28, hypersomnia was present in 25, in some cases severe. The patients so affected showed a characteristic absence of anxiety—they were level-headed, stolid, placid, imperturbable, and often dull; symptoms of neurosis were rarely present. Treatment was instituted with amphetamine ('dexedrine'), to

which the patients showed a remarkable tolerance, some reporting a good night's rest after a dose of 25 to 30 mg. taken at bedtime. In some cases a dose of 10 mg. at bedtime proved sufficient. The results of treatment were highly satisfactory; in four cases, of which detailed particulars are given, the enuresis was entirely controlled in two, and almost so in the other two. Similar results were obtained in the remaining 21 cases, although 'the patients have not been followed up long enough for a final conclusion to be reached'. It is stated that 'large doses are often necessary to effect cure or relief. No detrimental effects were seen'.

The Prevention of Vomiting Caused by Aureomycin

ONE of the practical disadvantages of aureomycin is its tendency to produce nausea and vomiting. To overcome this, L. G. Bartholomew and D. R. Nichols (*Proceedings of the Staff Meetings of the Mayo Clinic*, June 21, 1950, **25**, 370) recommend the use of milk. In four patients who were given a single dose of 750 mg. of aureomycin by mouth, the concentration of aureomycin in the serum ranged from 0.5 to 2.0 micrograms per ml., whilst in three patients who received the same amount by mouth every six hours for several days the serum levels ranged from 1.0 to 4.0 micrograms per ml. Four patients were then given 750 mg. of aureomycin and 30 ml. of 'an aluminium hydroxide gel', and the serum concentration of aureomycin was found in most instances to be 0.5 microgram per ml., and never exceeded 1.0 microgram per ml. Five patients were given 750 mg. of aureomycin and 200 ml. (one glass) of milk, and the serum aureomycin ranged from 0.5 to 2.0 micrograms per ml. Except in an occasional case the vomiting was controlled by the administration of milk. The unsatisfactory figures for the absorption of aureomycin when given with aluminium hydroxide gel are confirmed by J. C. Seed and C. E. Wilson (*Bulletin of the Johns Hopkins Hospital*, June 1950, **8**, 415), who found that 'the administration of aluminium hydroxide gel (0.3 ml. per kg.) with aureomycin (11 mg. per kg.) reduces the serum microgram-hours of aureomycin by 80 per cent. or more'. The Mayo Clinic workers conclude that 'the administration of milk with aureomycin therefore appears to be an acceptable method of reducing gastro-intestinal irritation and vomiting without interfering with the absorption of aureomycin into the serum'.

Paroxysmal Tachycardia in Infants

ALTHOUGH relatively uncommon, paroxysmal tachycardia in infants is a much more serious condition than in adults, as congestive heart failure is liable to develop more quickly. In infants it is usually supraventricular in origin. Details are given by W. M. Brownlee *et al.* (*American Journal of Diseases of Children*, May 1950, **79**, 838) of a case which responded dramatically to metacholine ('mecholyl'). The infant, aged ten weeks, was admitted to hospital with paroxysmal supraventricular tachycardia, the heart rate being 330 per minute. There was no response to pressure on the carotid sinus, the eyeball or the liver, or to digitalis. Finally, when the tachycardia persisted and the infant's condition became desperate, 1 mg. of metacholine was given subcutaneously. Within two minutes the heart rate had dropped to 140 per minute. A subsequent return of the tachycardia responded equally quickly to the same dosage, this time the rate falling to 70 per minute. Later less severe attacks were controlled by digitalis and sedation. It is recommended that atropine, which counteracts the effect of mecholyl, should be on hand in case of overdosage with mecholyl. It is concluded that 'metacholine has a place in the treatment of paroxysmal supraventricular tachycardia in infants, especially when other methods seem to have failed'. . . . Digitalis in adequate amounts should be given prophylactically for three months or longer following an attack of tachycardia'.

Bromide Intoxication

SIXTY-EIGHT cases of bromide intoxication were discharged from the Boston City Hospital during the period 1931-48. The case records of 27 of these patients have been analysed by H. A. Perkins (*Archives of Internal Medicine*, May 1950, **85**, 783). The chief complaints on admission to hospital were varying degrees of drowsiness, in five cases amounting to coma, and weakness. The most common symptom was weakness, which was present in 21 cases; in 12 cases it was confined to one arm or leg, whilst in three cases there was hemiparesis. Aches and pains were present in 11 cases. The physical signs included incontinence of urine (12 cases); disturbances of speech (20 cases); alterations of reflexes (20 cases); ocular disturbances (14 cases); ataxia (10 cases); excitement (21 cases); confusion (17 cases); hallucinations (12 cases); delusions (8 cases). Marked dehydration was common. A rash was present in over one-third of the patients. The most significant finding in the cerebrospinal fluid was a rise in the total proteins (average 55 mg. per cent.) which was found in nearly two-thirds of the cases. The bromide level in the blood ranged from 'a trace' to 380 mg. per cent. Treatment consisted of the administration of sodium chloride: up to 4 g. orally every four hours; this was supplemented by the parenteral administration of 4000 ml. of

isotonic sodium chloride every day. Sedatives were also given: paraldehyde, chloral hydrate, or barbiturates. The stay in hospital varied from four to forty days (average 17 days). It is stated that the possibility of bromide intoxication is not considered often enough in differential diagnosis, and the following statement is made: 'Physicians are initially responsible for approximately 50 per cent. of cases of excess bromide ingestion. Prescriptions for bromides should be non-refillable. The practice of self medication with bromo-seltzer should be condemned, particularly in view of its habit-forming properties'.

Vitamin E in Tropical Ulcer

Two cases of tropical ulcer successfully treated with vitamin E are recorded by A. Bierzynski (*Caribbean Medical Journal*, 1950, **12,** 5). Both patients were males, one with a five years' history of relapses following medical treatment and incision: initial treatment was penicillin for seven days (total 1,170,000 units), and sulphadiazine (total 32 g.), with wet dressings twice daily, following by a closed plaster of Paris cast. On the cast being removed eight weeks later there was no sign of epithelization. *a*-tocopherol, 300 mg. daily, was prescribed, with wet dressings. Three weeks later the ulcer had healed completely. The second case was similar, but the ulcer was of only fifteen days' standing. *a*-tocopherol, 300 mg. daily, with twice daily wet dressings was instituted. Four days later the ulcer was clean and filling up, and twelve days later had completely healed. The temperature of the affected foot in both cases rose from 90° to 93.6° F., and from 91° to 95° F. It is stated in conclusion that '*a*-tocopherol being in short supply and of a prohibitive cost in the Island it has not been possible to treat more than two cases', but 'were these findings confirmed by better equipped investigators, some progress would be made in combating an ailment which, by reason of its prevalence, is a very real social question in many tropical countries'.

Formaldehyde Treatment of Gastric Disturbances

According to S. Wagner (*Münchener medizinische Wochenschrift*, July 7, 1950, **92,** 524), oral administration of formaldehyde is useful in peptic ulcer and in irritable (vagotonic) stomach. Gastric secretion and acidity are diminished, emptying of the stomach is delayed, and secretion of mucus is stimulated. The unpleasant taste of the medicament is compensated for by prompt amelioration. In combination with parasympathicolytic and sympathicomimetic substances and with barbituric acid, formaldehyde produces complete gastric inactivity, secretory and motor. The author recommends 0.5 to 1 ml. of 35 per cent. formaldehyde solution in a tumbler of water, six to eight hours after the evening meal; first for three to four consecutive nights, then for two to three nights, and finally only when there is pain during the night.

Tetra-ethylammonium Chloride Therapy of Peptic Ulcer

In over 80 per cent. of 18 patients treated by A. L. C. Maggi and M. Meeroff (*Revista de Medicina y Ciencias Afines*, April 1950, **12,** 111) with intramuscular injections of tetra-ethylammonium chloride (15 mg. per kg. body wt.) for peptic ulcer, satisfactory results were obtained: the quantity of gastric contents and acidity decreased and nocturnal pain disappeared completely. The action is said to be due to blockage of transmission at the neurovegetative ganglion synapsis. In a further paper, A. L. C. Maggi, M. Meeroff and J. Anschütz (p. 131) studied the effect of the drug on gastric tone and movements: in 50 per cent. of patients tone was inhibited, and in over 90 per cent. contractibility was diminished. The medicament is recommended for the relief of pain due to gastric hypermotility, and its use is suggested in patients exhibiting the 'dumping syndrome' after gastrectomy.

Penicillin Dentifrices

The effect of a penicillin dentifrice upon salivary lactobacilli has been investigated by R. J. Fitzgerald *et al.* (*Journal of the American Dental Association*, July 1950, **41,** 62). Two groups of schoolchildren, aged six to fourteen years, were taught how to brush their teeth, and were given a tooth powder which was identical for the two groups, except that that given to one group contained 500 units of potassium penicillin per gramme of tooth powder. There were 181 children in the penicillin group and 129 in the control group. Lactobacillus counts were made after the children had been using the dentifrice for eighteen months and again six months later. The percentage of culture plates negative for lactobacilli at the end of these two periods was 18.8 and 20.8 for the penicillin group, and 21.4 and 17.7 for the control group. Neither was there any significant difference between the two groups in the percentage of penicillin-resistant lactobacilli: 14.4 per cent. in the penicillin group, and 10.8 in the control group. In other words, 'the use of the penicillin dentifrice did not result in a permanent decrease in salivary lactobacillus counts, nor did it result in an increased incidence of penicillin-fast lactobacilli compared with a control group using the same dentifrice except for the omission of penicillin'.

REVIEWS OF BOOKS

Recent Advances in Pharmacology. By J. M. Robson, M.D., D.Sc., F.R.S.E., and C. A. Keele, M.D., F.R.C.P. London: J. & A. Churchill Ltd., 1950. Pp. xi and 418. Figures 46. Price 24*s*.

This is a welcome addition to a popular series of textbooks. The author-partnership is a particularly happy one for the purpose—a laboratory pharmacologist and a clinical pharmacologist. The result is that the book can be strongly recommended to practitioners. Theory is not ignored, but the emphasis throughout is upon the more practical aspects of the problems, and upon human experiments rather than animal ones. The rapidly changing face of pharmacology makes it almost impossible to bring out a textbook that is up to date, but the authors have been unusually successful in their attempts. Most of the recent advances in pharmacology have been covered, but inadequate attention is paid to sympathomimetic drugs. The absence of any reference to recent work on gastrin, secretin, or urogastrone is a curious omission. Nor is insulin included, although the thyroid, and the steroids of the gonads and the adrenal cortex are covered. Space could have been found for these by omitting the chapter on bacterial chemotherapy and that on antrycide: the former especially, one scarcely expects to find in a book of this order. What there is, however, is good, and includes the anticholinesterase drugs, the antihistamine drugs, the chemotherapy of malignant disease, anticoagulant drugs, and hæmopoietic drugs. This is a book which is essential for the undergraduate and the postgraduate, but practitioners will also find it of value in bringing themselves up to date on the subject of the potent drugs which they are now prescribing for their patients.

Essentials of Urology. By J. C. Ainsworth-Davies, M.D., B.Ch., F.R.C.S. Oxford: Blackwell Scientific Publications, 1950. Pp. xi and 734. Figures 512. Price 50*s*.

Essential Urology. By Fletcher H. Colby, M.D. Baltimore: The Williams and Wilkins Company; London: Baillière, Tindall & Cox, 1950. Pp. vi and 580. Figures 342. Price 61*s*. 6*d*.

It is interesting to review these two books, one English, the other American, alongside, particularly when the titles of both indicate similar aims.

Mr. Ainsworth-Davies' book is up-to-date and the author achieves his objectives. These are to describe the essentials of diseases of the urinary and male genital tracts, their signs and symptoms, the general and special methods of examination and the appropriate methods of treatment. His description of cystoscopic orientation and interpretation of cystoscopic appearances will prove most helpful to the younger specialist. There is an excellent chapter on urinary disinfectants and diuretics, but the section on the benefits of streptomycin in genito-urinary surgery is over-optimistic: for example, the statement that tuberculosis of the epididymis and prostate responds in dramatic fashion to this antibiotic is contrary to the findings obtained in many careful investigations. Also open to question is the description of the pathology of renal tuberculosis, particularly the statement that the more common type first attacks the pelvis and calyces. Diseases of the prostate are dealt with in a well-balanced manner and no claims are made for exclusive merits of any one method of operative treatment. This readable textbook, well and profusely illustrated, reflects in a large measure the British urological viewpoint and should be particularly valuable to the junior surgical officer and the practising general surgeon.

Dr. Colby writes mainly for students, and accordingly, when dealing with treatment, deliberately limits himself to an outline of accepted methods. The first 90 pages are devoted to the embryology, anatomy and physiology of the genito-urinary organs. This is followed by a short section on the examination of the urological patient, in which great stress is laid on the method of history taking and ordinary physical examination before detailing the special urological procedures. Diseases of the genito-urinary organs are next discussed in turn. Each chapter in this section is enhanced by the emphasis laid on pathology. As is to be expected from a work based on urology as taught in Massachusetts General Hospital, this book attains a high standard of excellence, and is probably one of the best on the subject designed for the undergraduate.

Electroencephalography. Edited by Denis Hill, M.B., F.R.C.P., and Geoffrey Parr. London: Macdonald & Co. (Publishers) Ltd., 1950. Pp. vii and 438. Illustrated. Price 78*s*.

This work, the subtitle of which is 'A symposium on its various aspects', represents the combined effort of a group of authorities, each of whom is a recognized expert in his own particular field. The aspects of electroencephalography dealt with are grouped under the head-

ings—Technique, Physiology, Biochemistry, Pharmacology, Normal Rhythms, and the four clinical sections of Epilepsy, Intracranial Tumours, Cerebral Trauma, and Psychiatry. A valuable series of appendices includes recommendations for the setting up of an E.E.G. Laboratory, and an account of the equipment used both for recording and analysing the brain waves. The clinician will find that his natural interest directs his attention to the chapters dealing with normal rhythms and the changes seen in epilepsy, tumours and trauma. A further interesting section discusses the part played by the electroencephalogram in psychiatry. The writing in these chapters is characterized by its lucidity and there is, moreover, a refreshing appreciation of the limitations as well as the value of electroencephalography in clinical medicine. This work contains much of value for workers in all branches of neurology and its associated sciences, and the editors and their team of experts are to be complimented on an excellent publication.

Quinidine in Disorders of the Heart. By Harry Gold, M.D., New York: Paul B. Hoeber, Inc.; London: Cassell & Co., Ltd., 1950. Pp. x and 115. Price 16*s*.

Although one of the most useful drugs in cardiological practice, quinidine has always tended to be treated rather cursorily in textbooks of cardiology. There has for long been a need for a reliable monograph on the subject. This need has now been met by Professor Gold's 'practical manual', as he calls it. No one was better qualified to undertake the task, and clinicians will find in it a reliable guide to the use of the drug. The book is inherently practical and clinical in its approach. This is no theoretical discussion of a drug by a laboratory pharmacologist. So careful has the author been to emphasize the clinical aspects of the subject that the chapter which would normally be entitled 'pharmacology' is headed 'therapeutic actions'. This is undoubtedly the correct approach for the practising clinician. Those who have had much experience with quinidine will be interested in the author's comment that he has never encountered a patient with natural allergy to the drug. Needless to say, the teaching is sound, although not all cardiologists will agree with everything he says. For instance, the common practice in this country is to digitalize the patient with auricular flutter before switching to quinidine. Professor Gold prefers to start off with quinidine. Then again, the value of quinidine for controlling extrasystoles is problematical, and it is difficult to understand his reluctance to give quinidine intravenously in cases of paroxysmal ventricular tachycardia except *in extremis*. These, however, are merely differences of opinion. The book is one which should be studied carefully by all practising cardiologists and physicians.

Chemotherapie der Tuberkulose mit den Thiosemikarbazonen. By Gerhard Domagk. Stuttgart: Georg Thieme Verlag, 1950. Pp. vii and 405. Figures 257. Price DM. 60; $14.30.

The early chapters on pathology and experimental chemotherapy, the work of Domagk himself, are of a much higher standard than the later sections dealing with the clinical results of thiosemicarbazone treatment. Investigation of the possible occurrence of bacterial resistance has been surprisingly neglected, as also has a clinical comparison with streptomycin-treated cases. Nor were untreated controls used, although the shortage of streptomycin in the early years of the trial of thiosemicarbazone might well have justified such an experiment. The book is well produced and illustrated, and it is a pity that the clinical investigations are not precise enough for an accurate assessment of the value of thiosemicarbazone in tuberculosis to be made.

Postgraduate Gastroenterology. Edited by Henry L. Bockus, M.D. Philadelphia and London: W. B. Saunders Company, 1950. Pp. xix and 670. Figures 258. Price 50*s*.

This book is a record of the proceedings of a postgraduate course in gastroenterology held in Philadelphia. The course covered certain limited topics in this field which were presented as symposia and followed by discussion. The resulting record reveals a stimulating approach to recent thought in this specialty, and one can only be faintly envious of a country that can afford to immortalize a postgraduate course in such lavish form.

Among the Doctors. By Alfred Cox, O.B.E., LL.D., M.B., B.S. London: Christopher Johnson, 1950. Pp. 224. Illustrated. Price 12*s*. 6*d*.

In this book the former secretary of the British Medical Association recalls memories of his early days in the north-east of England and of his period of office with the B.M.A. He is happier in his reminiscences of industrial practice in the early years of the century than he is in those of the events in which he participated later in life. His account of the negotiations preceding the introduction of the National Health Insurance Service are particularly apposite at the present moment. Of his stories, the best, and probably appreciated by no one more than

by the victim, is that of the only time he saw Lord Horder blush. He has also an interesting account of the rudest speech he ever heard—delivered by the late Lord Birkenhead. Although it adds little fresh to our knowledge, the book is an interesting commentary on one of the most critical periods in the history of the medical profession in this country.

Office Orthopædics. By Lewis Cozen, M.D., F.A.C.S. London: Henry Kimpton, 1950. Pp. 232. Figures 156. Price 35*s*.

This book, well written and attractively got up with informative illustrations, sets out to be of help to general practitioners who have to apply simple orthopædic remedies in the surgery. One section consists of a catalogue of differential diagnoses of everyday complaints in the orthopædic field. Practitioners without specialist services will find the book the best of its type.

NEW EDITIONS

The second edition of *The British Encyclopædia of Medical Practice* (Butterworth & Co. (Publishers) Ltd., 60*s*.), Volume I of which is now published, appears under the general editorship of Lord Horder. This volume starts with 'abdominal emergencies' and ends with 'anus diseases'. On the whole, revision has been adequate, but it is disturbing to find stilbœstrol and dienœstrol recommended in the same dosage for the treatment of amenorrhœa, just as it is to find Blaud's pill and iron and ammonium citrate the only iron preparations recommended for administration to the pregnant woman. The section on amœbiasis is conventional in its approach, but the author is scarcely fair in his comments on the value of penicillin in amœbic dysentery. Incidentally, some of the illustrations in this section are disappointing in their standard of reproduction. Five pages seems rather a liberal allocation for 'ackee poisoning', especially when heliotherapy is dismissed in nine lines. A sixty-seven page index is an unusually generous allowance of space for this purpose, but fewer pages and more discrimination in the selection and arrangement of items would enhance its value considerably. The general standard of the book, however, is commendably high, and practitioners will find it of much value as a comprehensive, yet quick-reference, encyclopædia of medicine.

Emergencies in Medical Practice, edited by C. Allan Birch, M.D., F.R.C.P., in its second edition (E. & S. Livingstone Ltd., 27*s*. 6*d*.) appears less than two years after the original publication. Four new chapters have been added, dealing respectively with urgent aspects of skin diseases, eye diseases, anæsthesia, and the postoperative state. Another new feature is the inclusion of conversion tables showing the approximate metric equivalents of the common doses in the imperial system. The contributors to this work are all well-known names in the medical profession, and the Editor has succeeded in compiling a book of practical significance which should continue to be of great value to the general practitioner.

Medical Gynecology, by James C. Janney, M.D., F.A.C.S., in its second edition (W. B. Saunders Company, 32*s*. 6*d*.) is largely based on the author's experience in teaching clinical gynæcology at the Boston University School of Medicine: in his own words 'The scope of the book is limited to office gynecology. It has two aims. One is to aid the medical student in correlating didactic lectures with the experience obtained in the gynecologic clinic. The other aim is to provide refresher material for the general practitioner and to bring him up to date on the new developments in the field'. These aims the author has accomplished. Special features of the new edition are: a section on tests and special examinations; chapters on sterility, contraception, and endocrine therapy; a section on chemotherapy; and a useful chapter on physical examination. The work is well produced and richly illustrated.

The third edition of *Food Poisoning: Its Nature, History and Causation: Measures for Its Prevention and Control*, by Elliot B. Dewberry, M.B.E. (Leonard Hill Ltd., 17*s*. 6*d*.) contains, among new material, sections on ice cream poisoning, food handling, and hygiene, and also an appendix dealing with gastro-enteritis aboard ship. Appendix I deals with the Ministry of Health Memo. 188 (revised 1949), which gives the steps to be taken in England and Wales by Medical Officers of Health in the investigation of food poisoning. Poisonous plants and fungi are particularly well illustrated.

A Pocket Obstetrics, by Arthur C. H. Bell, F.R.C.S., F.R.C.O.G., in its second edition (J. & A. Churchill Ltd., 7*s*. 6*d*.). Among the new additions is a section on the use of penicillin in puerperal sepsis.

Aids to Psychiatry, by W. S. Dawson, D.M., F.R.C.P., F.R.A.C.P., D.P.M., in its sixth edition (Baillière, Tindall & Cox, 6*s*.) contains two new chapters: on personality, and child psychiatry. In view of the present increase in juvenile delinquency the latter is a useful addition to this compact and practical treatise on psychiatry.

The contents of the October issue, which will be a special number devoted to "Advances in Treatment", will be found on page lxiii at the end of the advertisement section.

Notes and Preparations, see page 313
Fifty Years Ago, see page 317.

Bismuth Salts are Now Freely Available

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Extract from report:

The dietetic and medicinal treatment—'combined bismuth and mineral water therapy' was carried out on all 315 patients on the principles laid down above. Provisional results, shown by Table 1, are very satisfactory, since 84.8% (267) cases remained free of symptoms.

TABLE 1

Period under observation	Number of patients	Free of symptoms	Some improvement	No improvement	Relapses
1 month	8	3	0	5	0
1-2 months	8	8	0	0	0
2-4 months	36	30	3	3	2
4-6 months	248	211	20	17	5
Treatment begun recently	15	15	0	0	0
TOTAL	315	267	23	25	7

(1948): 'Massive Doses of Bismuth Subcarbonate in the Treatment of Ulcer,' *Nordisk Medicin*, **40**, 1979 (Oct. 29); abstract *J. Amer. Med. Ass.*, 1949, **139**, 1234 (Apr. 23).

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NOTES AND PREPARATIONS

NEW PREPARATIONS

LYTENSIUM (pentamethonium bromide) and VEGOLYSIN (hexamethonium bromide) are ganglion blocking agents. The use of the former is indicated in peripheral vascular disorders, hypertension, and for the reduction of hæmorrhage during operation. The latter has been found effective in the treatment of peptic ulceration, and in all types of hypertension. 'Lytensium' is issued in 10 per cent. solution, in boxes of 10 ampoules of 1 ml., for intramuscular injection, and in the form of a syrup for oral administration, in bottles of 4 and 40 fluid ounces. 'Vegolysin' is also issued in 10 per cent. solution for intramuscular injection, and in tablet form for oral administration, in containers of 50 and 500 tablets of 0.25 g. (May & Baker Ltd., Dagenham, Essex.)

XYLOCAINE (α—diethylamino—2,6—dimethylacetanilide) is a new local anæsthetic, obtainable as 'xylocaine (plain)' and 'xylocaine (adrenaline)'. Their use is indicated in surgery, for infiltration, block and surface anæsthesia; in dentistry; and therapeutically, for sympathetic nerve block. Xylocaine (plain) 0.5, 1 and 2 per cent., and Xylocaine (adrenaline) 0.5, 1 and 2 per cent., are supplied in sterile rubber-stoppered vials of 20 ml., in boxes of 6. (Duncan, Flockhart & Co. Ltd., 155-7 Farringdon Road, London, E.C.1; 104-8 Holyrood Road, Edinburgh, 8.)

TUINAL and AMESEC.—These two preparations, which have hitherto been supplied in two-colour capsules, will now be issued in capsules of a single colour: 'tuinal' (light green), and 'amesec' (orange). (Eli Lilly & Co. Ltd., Basingstoke, Hants.)

AVAILABILITY OF BISMUTH

MR. A. DUCKWORTH, Acting Secretary of the Association of British Pharmaceutical Industry, writes:—

'In the article on "Favourite Prescriptions in General Practice" contributed to your July 1950 issue by Dr. Hugh Barber, it is stated (p. 12) that bismuth carbonate is difficult to obtain. It is true that during and immediately after the war years there was a shortage of bismuth salts in this country, but this situation no longer obtains, and plentiful supplies both of bismuth carbonate and other bismuth salts are now available.

We appreciate that the busy practitioner may not have become aware of this, and we should therefore like to assure your readers that no difficulty will now be encountered by the pharmacist in dispensing prescriptions which include bismuth salts'.

NEW HEARING AID

THE AMPLIVOX MODEL KA is a new hearing aid with automatic volume compression (A.V.C.), designed to limit the maximum sound intensity for those unable to tolerate it, and also to avoid overloading with its consequent distortion. In the Model KA Amplivox, a flat response microphone and earphone are used with A.V.C. applied at two alternative levels selected by means of a switch: the minimum A.V.C. position limits output to about 5 dB below maximum; in the maximum position output is limited at 10 dB lower still. The former is for use in avoiding distortion; the latter for those cases of deafness with only low tolerance for sound. The aid, which measures 5 in. by 2 $\frac{4}{16}$ in. by $\frac{3}{4}$ in., is contained in a smoothly surfaced, die cast aluminium case finished in polychromatic lacquer. The weight, complete with batteries, is 6$\frac{1}{2}$ ounces. Two types of miniature earphones are available for use with the aid: Type E/3W, with frequency range of 125-4000 C.P.S., and Type E/3L, with a greater sensitivity to low frequencies combined with high frequency cut off at 2,500 c.p.s. A bone conductor is also available. Price 25 guineas complete. (Amplivox Ltd., 2 Bentinck Street, London, W.1.)

B.M.A. MEDICAL EXHIBITION LIVERPOOL

BECAUSE of the numerous counter-attractions in the shape of scientific and social events the Medical Exhibition at the B.M.A.'s annual meetings seldom draws such crowds as the one held in London in November each year. But of the exhibitors in Liverpool last July it could not be asked 'why stand ye here all the day idle?', for there was certainly no lack of interest in their wares. St. George's Hall made an impressive setting for the Exhibition, comparing favourably with the hot-house atmosphere of Harrogate last year. The Official Catalogue fully describes the instruments, drugs, foods, and books shown. This account presents some personal impressions and briefly lists a few novelties. Among the most striking display pieces were 'The Transfusion Safety Stakes'

CONTINUED ON PAGE 314

(Crookes)—the five runners, each a horse in the form of the standard M.R.C. transfusion bottle; the six jumps—obstacles to be overcome by the ideal transfusion solutions; and a working model of a menstrual clock, showing the relative circulating levels of five sex hormones, together with the endometrial changes (British Schering). The new drugs included the bactericide *Bradosol* and the pocket nebulizer *Antistin-Privine* (Ciba); *Landrax* (cytochrome C) and *Rondase* (hyaluronidase)—both Evans Medical; *Neo-Epinine* and *Histantin* (Burroughs Wellcome); *Avloprocil* (procaine penicillin G) and *Avlosulfon* (diaminodiphenylsulphone)—both Imperial Chemical (Pharmaceuticals); *Eshamel* and *Pendex* (Menley & James); *Pregnenoline*—a steroid approaching cortisone in action, and the *Glucotest* outfit (B.D.H.); *Sedulon* and *Thephorin* (Roche); *Seclopen* (Glaxo); *Hexathide* and *Dimethyltubocurarine iodide* (Allen & Hanburys); two methonium compounds *Vegolysin* and *Lytensium* (May & Baker); *Penotrane* and *Sterathal*—a new oral sulphonamide (Ward, Blenkinsop); *Histostab* (Boots); and *Lextron*—now freely obtainable in this country (Eli Lilly).

BLESMA

TWELVE THOUSAND limbless ex-Servicemen are united in comradeship and service in 102 branches of the British Limbless Ex-Service Men's Association, each branch having its own Employment and Welfare Committees. As many badly wounded men are too proud to divulge their troubles, organizations, doctors, and others are invited to refer to BLESMA details of those who need a helping hand. Donations may be sent to Lord Willoughby de Eresby, 25 Charles Street, London, W.1. (General Secretary, 37 Anson Road, Victoria Park, Manchester, 14.)

SCIENTIFIC FILM ASSOCIATION

THE following publications have been received: two pamphlets giving the history and objects of the Association; an account of the Third Congress of the International Scientific Film Association held in Brussels last year; descriptions of scientific films, including 'Fly about the House,' 'The Common Cold', and 'Liver Fluke in Great Britain'. The Association, which is anxious to increase its membership, exists to promote a wider understanding of science and of the scientific outlook by means of films. It issues catalogues and lists of films and arranges booking of films for its members. (4 Great Russell Street, London, W.C.1.)

The Medical Film Institute in New York has recently received a grant of over $20,000 from the Rockefeller Foundation for cataloguing 5000 films on medical subjects.

N.O.T.B. ASSOCIATION

THIS Association was formed in January 1949 to carry on the work of the old National Ophthalmic Treatment Board. All ophthalmic medical practitioners whose names are on the Central Professional List, and all dispensing opticians who are members of the Guild of British Dispensing Opticians, are eligible for membership. The annual subscription is one guinea. The objects of the Association are: to facilitate medical eye examination for the general public; to preserve the liaison between ophthalmic practitioners and dispensing opticians; to encourage the development of adequately equipped and staffed Eye Centres in areas where the Permanent Eye Service is not in operation. (Tavistock House North, London, W.C.1.)

PUBLICATIONS

Use of Chemical Tests for Alcohol in Traffic Law Enforcement.—In Publication No. 50 of the *American Lecture Series*, Glenn C. Forrester, Ph.D., within the compass of 90 pages, discusses the rôle of alcohol in accidents ('in traffic deaths and injuries the drinking pedestrian must not be forgotten in assessing blame'), its action on the nervous system, variations in effects on different persons, and chemical tests for alcohol. These tests are now mandatory in Sweden and in other European countries. The views of certain American organizations are quoted on their value, and a number of legal cases are mentioned. The final chapter is devoted to the 'intoximeter' (the author is Manager of the Intoximeter Association, Niagara Falls)—an instrument for measuring the amount of alcohol in the breath. (Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd. 1950. Price 15s.)

The Scourge of Rheumatism.—This is the report of a conference held by the British Rheumatic Association in London in September 1949 and contains an introduction by Lord Horder; a paper by Dr. W. S. C. Copeman, 'Modern Views on the Treatment of Rheumatoid Arthritis'; discussions on 'The Care of the Rural Patient', 'The Disabled Persons Employment Act and the Rheumatic Sufferer', and 'Remploy Ltd'; and a symposium on 'The Problems and Employment of the Housebound Rheumatic Sufferer'. The book concludes with four papers on 'What Voluntary Organizations are Contributing'. (William Heinemann (Medical Books) Ltd., London, 1950. Pp. 85. Price 5s.)

CONTINUED ON PAGE 316

THE VITAMIN HOUR

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N.I.D. Booklet Number 481 is the National Institute for the Deaf Approved List of Dealers in Aids to Hearing. It has been compiled as a guide to deaf persons wishing to buy hearing aids, and the manufacturers and suppliers listed have entered into an agreement with the National Institute for the Deaf as to methods of trading. In the general preface it is stated: 'If deafened persons are advised to consider the purchase of an aid they should deal only with one of the manufacturers or suppliers given in this booklet'. The necessity for deaf persons to study lip-reading is also stressed, and a textbook on the subject, 'Lipreading,' by J. H. Burchett, is available, price 6*s.* 6*d.* (National Institute for the Deaf, 105 Gower Street, London, W.C.1.)

THE *Report on the Health of the City of Manchester for* 1949 is one of which the medical officer of health and his staff have every reason to be proud. Although the crude death rate was 12.91, compared with 12.27 for 1948, the infant mortality rate, at 38.24 per 1000 live births, was 3.88 lower than in 1948, and the lowest ever recorded in Manchester. There were no deaths from diphtheria during the year. The number of children who have received a full course of immunization against diphtheria represent 61.76 of all children in the age-group 0-5 years, and 75.77 of those in the age-group 5-15 years. The percentage of children successfully vaccinated against smallpox was only 22.52, compared with 36.81 in 1948, and 61.11 in 1946. The tuberculosis position is as distressing as anywhere in the country: 'the increase in the number of new cases of tuberculosis, and the continued extreme shortage of sanatorium beds for adults, has led to a year of frustration'. The average waiting period for male beds is eleven months, and for females, seven months. On December 31, 1949, 653 patients were undergoing treatment in sanatoria and hospitals, and 322 were awaiting admission.

75 *Vegetarian Savouries*, by Ivan Baker. In the days of long dinners, it is explained, the 'savoury' was a salty, cheesy, or smoky morsel served at the end of the meal to bring an overworked palate to rest. The savouries in this collection are substantial protein dishes, intended to form the main part of the dinner. (The Vegetarian Society, Bank Square, Wilmslow, Manchester. Price 1*s.*)

Home Helps.—A booklet issued by the National Association for the Prevention of Tuberculosis points out that tuberculous patients are recognized as qualifying for the services of Home Helps and that, when sensible precautions are taken, there is little danger of infection. (NAPT, Tavistock House North, London, W.C.1.)

International Dental Journal.—The International Dental Federation announces the publication this month (September) of a new quarterly review in English of recent advances in dental science and practice. (Distributors Cassell & Co. Ltd., 37/38 St. Andrew's Hill, London, E.C.4. Single issues 12*s.* 6*d.*; £2. 5*s.* per annum post free.)

Glaxo Volume.—The third number of this 'occasional contribution to the Science and Art of Medicine' contains articles on calciferol in the treatment of lupus vulgaris, angiocardiography, and thyroxine, and a coloured portrait of Sir Alexander Fleming. The journal is attractively produced and beautifully illustrated.

Eli Lilly Price List.—We have received from Eli Lilly & Co., Ltd., a complete alphabetical price list of pharmaceutical products, dated June 1950. (Basingstoke, Hants.)

OFFICIAL PUBLICATIONS

Central Health Services Council.—The Central Health Services Council, set up under the National Health Service Act, acts as a body of confidential advisers to the Minister of Health. Its first report for the period ending December 31, 1949, discusses among other matters, health centres, hospital administration, prescribing, general practitioner obstetricians, cooperation between doctor and midwife, and organization of tuberculosis services. (H.M. Stationery Office, London. Price 1*s.*)

The Cause of Blindness in England and Wales, by Arnold Sorsby, M.D., F.R.C.S. After giving statistical figures of blind persons in the past (1851-1911), and the causes of blindness in those days, the author passes on to present-day analyses, first dealing with the causes, age and sex distribution, as shown by blind certificates, and then discussing the problems of the present-day blind population. (*Med. Res. Coun. Mem.* No. 24. H.M. Stationery Office, 1*s.* 6*d.*)

Domestic Science and Dietetics.—No. 13 of the *Choice of Careers* booklets, prepared by the Ministry of Labour and National Service and the Central Office of Information, and issued by the Central Youth Employment Executive, presents succinct, practical information on canteen catering in industry, hospitals, and the like: the work of the hospital dietitian; personal qualities required for such careers; and courses of training, with costs, openings, and salaries. (H.M. Stationery Office, London, 1950. Price 9*d.* net.)

THE PRACTITIONER: 50 Years Ago. See page 317

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THE PRACTITIONER

Fifty Years Ago

'Experience is the name every one gives to their mistakes'.—Oscar Wilde: *Picture of Dorian Gray*.

SEPTEMBER, 1900

WITH the last annual meeting of the B.M.A. in Liverpool but a pleasant memory, it is instructive as well as amusing to glance at an Editorial comment on the conference held fifty years ago at Ipswich, which 'seems to have been more lively than edifying . . . Disinterested outsiders were not a little startled by the exhibition of angry passions raging in the celestial souls of members of a profession which is supposed to be overflowing with the milk of human kindness. Doubtless the milk was soured by the disturbed state of the moral atmosphere . . . We are by this time well accustomed to violent and often foolish attacks on the Council, and, of course, a council may be considered fair game, as it can bear language as sulphurous as that of the Archbishop of Rheims on a famous occasion without anyone being a penny the worse. But editor-baiting is a novelty in these annual entertainments . . . Editors, of course, being human are not infallible, but it will be impossible to find any man of ability and self-respect to take charge of the *Journal* if he is to be made a target for criticism and invective by anyone who thinks he has a grievance against the Council . . . As the British Medical Association depends for its existence on the *Journal*, it is of the highest importance that the editor should be supported by the Council. To strike at the Council through the editor may not be a chivalrous proceeding, but for the Council to sit in Olympian serenity and allow him to be used as a whipping-post for its misdeeds is cowardly as well as undignified'.

The death of Sir William Stokes is described as 'one of the heaviest losses of this wretched South African war . . . To all the world he was known as one of the brightest lights of modern surgery, as an orator with hardly an equal in the profession which he adorned, and as a writer whose productions were always remarkable for beauty of literary form as well as by the solid value of their matter'. Sir William Stokes, who died of pleurisy at Pietermaritzburg, was the son of the Dublin physician William Stokes of Cheyne-Stokes respiration fame. President of the Royal College of Surgeons in Ireland, he is eponymously commemorated in the Gritti-Stokes operation (amputation through the articular end of the femur).

The annotation entitled 'Some Humours of Bacteriology', is delightful and worth reading in its entirety: 'In these days we are taught that the beginning of hygienic wisdom is the fear of the microbe. Accordingly every bacteriologist deems it a point of honour to discover at least half a dozen new species, and consequently scarcely a week passes without the world being warned of a new danger from some unsuspected source . . . The latest danger signal . . . is that hoisted by Dr. Orlandi, of Turin. There is biblical authority for the fact that death was once threatened to every man that empties his bladder against the wall. If we are to believe Dr. Orlandi this might very well occur owing to the

Sir William Stokes, M.D., F.R.C.S.I.

splashing of microbes from the wall on to the garments of the man thus relieving his feelings. He has made experiments with strict scientific precautions in a number of public urinals, and has been rewarded by an extensive and varied catch of microbes. Dr. Orlandi has no doubt that in this way the gonococcus might find a lodgment in the virgin soil . . .'.

The 'Original Communications' include an address by Victor Horsley on the surgical treatment of trigeminal neuralgia, and a paper by

FIFTY YEARS AGO—*continued*

H. Campbell Thomson on 'Some Disorders of Memory associated with Epilepsy, with special reference to "Reminiscences" '.

The recent bicentenary of Goethe's birth stimulated the production of a large number of articles dealing with the poet's relations to medicine, and it is interesting to find in the 'Literary Gossip' corner fifty years ago a reference to a monograph on this subject by Dr. P. H. Gerber of Königsberg. Owing to the incompetence of the midwife who attended his mother, Goethe 'narrowly escaped a very premature termination of his career . . . This accident induced his grandfather to introduce a law making the instruction of midwives compulsory'. Severely attacked by smallpox as a child, the poet in later life took an active part in introducing the practice of inoculation into Germany. At Strassburg he studied chemistry, anatomy, and medicine more assiduously than his proper subject—law. The left side of his face is said to have been longer than the right; the right eye was deeper, and he possessed a prominent nose. 'Professor Lombroso will doubtless give him a place in his Inferno of degenerates of genius'.

'Warning against some of the Evils of the Profession of Medicine' was the unusual title of an oration on medicine delivered at the annual meeting of the American Medical Association by Dr. J. A. Witherspoon of Nashville, Tennessee, and among the evils particularly specified was the 'useless multiplication of books': 'Every progressive man in the Profession feels the necessity of keeping abreast of the times, and when a new book is published will purchase it for fear he may lose some valuable information. Too often, however, the eager seeker after knowledge finds them poor copies without an original thought, with no necessity or reason for their existence. There is a prevailing tendency amounting almost to mania in young men to rush into print . . . Their proper sphere should be the medical journals, which are after all the greatest educators of the practitioner. In this sentiment we heartily agree with Dr. Witherspoon; only we venture to suggest that the young men . . . should read the journals before making them the medium for the conveyance of their new and original ideas to the pensive public. If they are in any doubt as to which would be the best to subscribe to, let them try *The Practitioner*'. W.R.B.

"66 . . . . In view of these analytical and general evidences this brandy may be described as particularly suitable for medicinal purposes." 99

See "LANCET" July 22nd 1899 p. 219

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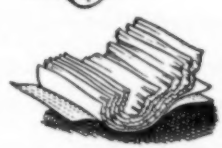

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THE PRACTITIONER

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